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500. L. Den Drijver, C. W. Holzapfel, J. M. Koekemoer, G. J. Kruger, and M. S. Van Dyk, Regioselective oxidation of carbohydrates triols: facile synthesis of 2,3-*O*-isopropylidene-β-D-*threo*-hexo-2,4-diulo-pyranose and 1,2-*O*-isopropylidene-β-D-*threo*-hexo-2,5-diulo-pyranose, *Carbohydr. Res.*, 155 (1986) 141–150.
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OXIDATIVE REACTIONS AND DEGRADATIONS OF SUGARS AND POLYSACCHARIDES*

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This article updates the treatment of this subject by J. W. Green[1] in the 1980 second edition of "The Carbohydrates, Chemistry and Biochemistry," edited by W. Pigman and D. Horton, and follows the same general layout of topics. While the emphasis is on newer material, the fundamental concepts of sustained importance are included. Where appropriate, the reader is directed to Green's original article for additional details on individual topics.

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I. Introduction

The oxidation of carbohydrates is an important tool for obtaining compounds having interesting chemical and physical properties. Such oxidation products constitute useful intermediates for the synthesis of more complex molecules, and they also display, in many cases, varied biological activities. The oxidation at the anomeric center and of the hydroxymethyl group of monosaccharides is well documented. Selective oxidation of primary hydroxyl groups or the glycolic oxidation of polysaccharides yields polycarboxylates having thickening, gel-forming, and metal-sequestering properties.

Oxidation in organic chemistry refers to the elimination of hydrogen atoms from a substrate, or to the replacement of a hydrogen atom bonded to carbon by a more electronegative element, oxygen in particular. As a more general concept, the oxidation of an organic compound involves the transfer of electrons from the substrate to the oxidant, a process that is usually accompanied by the breaking of carbon–hydrogen or carbon–carbon bonds. Such a reaction, which can formally be regarded as occurring between a nucleophile (the substrate) and an electrophile (the oxidant), is greatly affected by factors that alter the nucleophilicity or electrophilicity of the respective reactants; steric effects are often also important. A brief discussion of these factors is given first, and more-specific examples, together with mechanistic aspects and synthetic applications of these reactions, are presented in Sections II–XIII. These subjects have been previously reviewed,[1-4] and they are also discussed in the preceding article on oxidation products.

1. Heterolytic Oxidations

The two-electron oxidation of a secondary alcohol group can be regarded as an elimination of two hydrogen atoms and the formation of a double bond between the carbon atom and the oxygen atom. Equation (*1*) illustrates breakage of a C–H bond with elimination of a nascent hydride ion; this anion is a poor leaving group, but its removal is aided by the

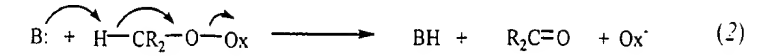
oxidant, which captures the pair of electrons and converts the hydride ion into a proton.

(*1*)

The O–H bond dissociates with the liberation of a proton; this bond-breaking is readily accomplished with the aid of a base, usually the solvent. Thus, the breaking of the C–H bond is generally the slow (rate-determining) step of the reaction.

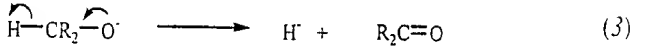
In principle, the flow of electrons shown in Eq. (*1*) can also occur in the reverse direction, with elimination of the hydrogen atom from the hydroxyl group as a hydride ion. Evidence for such a mechanism has been given.[5,6]

The oxidant may aid the elimination in a concerted or E_2 type of mechanism, as illustrated in Eq. (*1*); for such examples, the oxidant is not bonded to the substrate, except possibly in the transition state. Other oxidants, for example chromic acid, have been shown to form intermediate esters such as 1 (although other mechanisms have been proposed[7]), which subsequently decompose by a related, bimolecular elimination [Eq. (*2*)]; here the leaving group is the reduced form of the oxidant, and the C–H bond must necessarily break with the liberation of a proton. As in Eq. (*1*), the capture of electrons by the oxidant is the driving force of the reaction, so that the breaking of the C–H bond occurs simultaneously in the rate-determining step (Scheme 1).



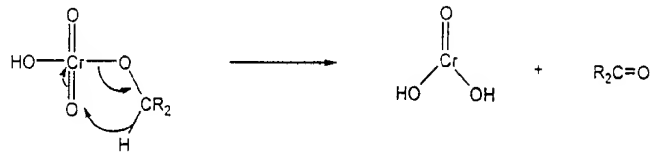
(*2*)

Variations of the foregoing two reactions are often encountered. Alkoxide ions, being relatively strong bases, can be considered to be reducing agents,[8] as they are able to eliminate hydride ions [Eq. (*3*)].



(*3*)

Glycols are more acidic than monohydric alcohols[9] and the C-1 group on an aldopyranoid compound is even more acidic, owing to the inductive effect of the ring-oxygen atom; therefore, sugars are more readily oxidized than ordinary alcohols. For the free sugars, however, oxidations at higher pH are accompanied by competing processes of epimerization and of degradation to saccharinic acids; this factor is discussed in Section II (see also preceding chapter).



1

SCHEME 1

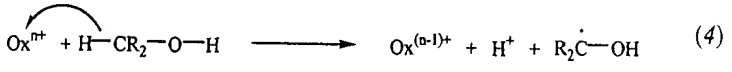
2. Steric Effects

The β anomers of sugars are generally oxidized more rapidly than the α anomers (see later), a similar pattern is seen in the faster oxidation of β-glycosides. The different rates of oxidation of β-D-glucopyranosides and their α-D anomers have been attributed to the equatorial orientation of the anomeric hydroxyl group in the $^4C_1$ conformation of the former. Other compounds have shown a similar behavior.[10] Thus, the relative rate of oxidation of *cis*-2-*tert*-butylcyclohexanol (HO-axial) with respect to the *trans* isomer (HO-equatorial) is approximately 5:1.

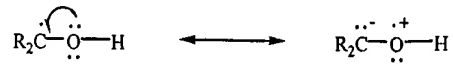
The oxidation of a secondary hydroxyl group of glycopyranosides involves the conversion of a tetrahedral carbon atom into a trigonal one, and there may be some resistance to the introduction of this constraint into the ring. Baker and Haines[11] pointed out the greater ease of oxidation of acyclic than of cyclic sugar derivatives; however, more-powerful oxidants may give good yields of glycosiduloses.[12]

3. Homolytic and Electron-Transfer Oxidations

As termolecular reactions are very rare, the transfer of two electrons must necessarily occur in two successive steps in reactions of one-electron oxidants. The first step is the formation of a radical [Eq. (*4*)]; the oxidant facilitates removal of the hydrogen atom, converting it into a proton. Resonance stabilization [Eq. (*5*)] of the resulting radical is regarded as more important than inductive effects. For stabilization of the radical, an adjacent atom (such as oxygen) having unshared pairs of electrons is necessary; therefore, initial attack generally occurs at a C–H bond adjacent to an oxygen atom, rather than at an O–H bond adjacent to a saturated carbon atom, which is incapable of participating in resonance stabilization. Thus, alkoxy radicals are electrophiles and they preferentially attack C–H bonds with high HOMO energies, for example the α-C–H bond of ethers and alcohols.[13] This is illustrated by the favored catalytic oxidation of glycosides having axially attached hydroxyl groups, because the attack is initially upon the sterically more available equatorial C–H bonds.



(*4*)

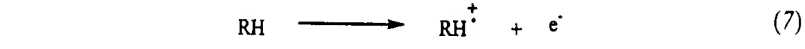


(*5*)

(*6*)

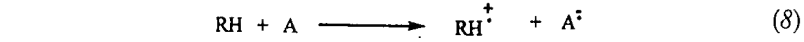
The final step is homolysis of the O–H bond in the radical to afford the carbonyl product plus a second hydrogen radical, which is converted by the oxidant into a proton [Eq. (*6*)]. Equation (*4*) is the slow or rate-determining step; removal of the second hydrogen atom is rapid.

Electron-transfer oxidation of organic compounds involves multiple steps with transient radicals as key reactive intermediates.[14] The electron-transfer oxidation of a neutral, diamagnetic organic donor (RH), having an even number of electrons, produces a radical cation, as shown in Eq. (*7*).



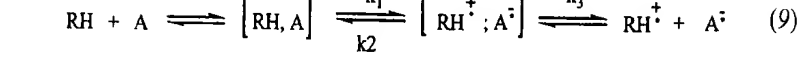
(*7*)

The energetic basis for the electron-transfer oxidation includes the thermodynamic potential of oxidation (E°_{ox}) for the electron transfer from RH in Eq. (*7*). Such an electron detachment is commonly effected at an electrode, by an oxidant, or with light. The oxidation is driven electrochemically by the anodic electrode potential, which matches the E°_{ox} value. Likewise, the driving force in the chemical oxidation of RH is provided by the redox potential (E°_{red}) of the electron acceptor or oxidant (A) according to Eq. (*8*).



(*8*)

Electron-transfer oxidation can be considered to consist of a series of equilibria as shown in Eq. (*9*), with formation of an electron donor–acceptor precursor complex, which leads to the contact ion-pair constrained by the solvent cage. Intermolecular reactions of $RH^{+\cdot}$, which lead to oxidation products, take place after escaping from the cage.[14]



(*9*)

Photochemical electron-transfer can be effected by irradiation of the charge-transfer absorption band of the electron donor–acceptor complex.[15] Alternatively, photochemical electron-transfer may proceed by actinic activation of RH followed by quenching with A, or by the reverse sequence involving activation of A and quenching with RH.

4. Electrophilic Nature of the Oxidant

Although the effect of increasing pH, already mentioned, is to increase the susceptibility of the substrate to oxidation, this increase generally decreases the effectiveness of the electrophilic oxidant at the same time. Permanganic acid is more effective than the permanganate anion as an oxidant.[16] Wet

combustions, the complete oxidation of organic compounds under strongly acidic conditions to carbon dioxide and water, may occur because of the extreme electrophilicity of the protonated oxidant. Thus, the two extremes of pH, extremely strong acid and extremely strong alkali, favor complete oxidation.

The effectiveness of an oxidant as an electrophile is roughly proportional to its "acidity" or lack of basicity. Phenylhydrazine, a weak base, is a very weak oxidant; however, substitution of nitro groups on the aromatic ring decreases the basicity and increases the potency of the hydrazine as an oxidant.

Another factor is the leaving-group ability, which is of importance in oxidations by peroxides and halogens. Such oxidants, reacting with a substrate S, tend to form an HO^+ or X^+ cation in the transition state and lose the rest of the molecule as an anion [Eq. (*10*)]; the more effective as a leaving group is X^-, the better is HOX or X_2 as an oxidant. Hydrogen peroxide, which must displace a strongly basic OH^- group, is a poor oxidant, whereas peroxyacetic acid, which reacts to displace the resonance-delocalized acetate anion, is a good oxidant. The nucleophilic nature of the sulfinyl oxygen of sulfoxides, and the good leaving-group properties of dimethyl sulfide, have been used effectively for the oxidation of primary and secondary hydroxyl groups (see Section IX).

$$S + HO{-}X \longrightarrow S{\cdots}HO^{+}{\cdots}X^{-} \qquad (10)$$

Oxidants often tend to disproportionate by interaction of the acidic or undissociated oxidant with the anion of the same oxidant;[1] this is a nucleophilic displacement, by the OX^- anion, of X^- from the oxygen atom of the electrophilic HOX [Eq. (*11*)]. Two points should be emphasized here. First, the maximum decomposition occurs when HOX and OX^- are in equal concentrations, that is, when the pH of the reaction is equal to the pK_a of the oxidant [Eq. (*12*)]. Second, since this is a displacement, the reaction goes more readily when the group X^- is easily displaced; thus formation of iodate from hypoiodite is more extensive than chlorate formation from hypochlorite.

$$2\,OX^- + HOX \longrightarrow 2\,X^- + HXO_3 \qquad (11)$$

$$K_a = [H^+]\frac{[OX^-]}{[HOX]} = [H^+];\quad pK_a = pH \qquad (12)$$

Although the examples illustrated in Eqs. (*1–6*) and (*10*) are given as secondary alcoholic groups, primary alcoholic groups can be treated similarly. Oxidation of the anomeric carbon atom in reducing sugars

($H{-}CR_2{-}OH$ grouping) proceeds much as for a secondary hydroxyl group. Oxidation of an $H{-}CR_2{-}OMe$ grouping (e.g., in an aldoside) is, however, quite different, because the readily displaceable hydrogen atom has been replaced by a methyl group, which is eliminated with great difficulty. Thus, oxidative attack on aldosides often takes place on available secondary or primary alcoholic groups, rather than on C-1.

II. Halogen Oxidations

Bromine (hypobromite) and hypoiodite oxidations are particularly useful for the preparation of aldonic acids from aldoses and of aldaric acids from glycuronic acids. Primary alcohol groups also undergo oxidation by these reagents, although this conversion is of less value; glycosides can thus be converted into glycosiduronic acids, and alditols into aldoses and aldonic acids.

Secondary alcoholic groups are slowly oxidized to ketone groups, and 2-glyculosonic and 5-glyculosonic acids are formed in this way. More-extended oxidation results in the cleavage of carbon–carbon bonds and in the production of chain-shortened acids.

The halogens and their oxyacids, particularly chlorine and hypochlorous acid, are widely used as oxidizing and bleaching agents. These properties are related to the variations of redox potentials.[17]

1. Halogens and Hypohalites

The oxidation with halogens and hypohalites is a complicated reaction, as it depends strongly on the conditions of temperature, acidity, and concentration of the reacting species. The halogens show considerable differences in the positions of the various equilibria and the speed with which the equilibria are attained (see Table I). In acidic solution, the equilibrium between free halogen and hypohalous acid [Eq. (*13*)] lies far to the left, and the concentration of hypohalous acid is very low. When alkali is added to the system, the concentration of hypohalite ion increases, according to Eq. (*14*).

$$X_2 + H_2O \rightleftharpoons HOX + HX \qquad (13)$$

$$X_2 + 2\,OH^- \rightleftharpoons OX^- + X^- + H_2O \qquad (14)$$

Hence, the concentrations of free halogen, halic acid, and hypohalite vary greatly with the acidity. For example, at pH 1, the total chlorine present

TABLE I
Selected Properties of Halogens, Halides, and Hypohalous Acids

Halogen	Cl	Br	I	References
Solubility of X_2 in water (mol/L) at 25°C	0.092	0.2141	0.013	18
K for $X_2 + H_2O \Leftrightarrow HOX + HX$	4.5×10^{-4}	2.4×10^{-8}	3.6×10^{-13}	1
k, in sec^{-1}, for $X_2 + H_2O \rightarrow HOX + HX$	11	110	3	1
pK_a, for $HOX \Leftrightarrow H^+ + OX^-$	7.40	8.55	10.5	1
E_0, in volts, for $2X^- \Leftrightarrow X_2 + 2e^-$	−1.356	−1.065	−0.535	18
Leaving-group tendency, k_x/k_{Br} (average)	0.02	1.0	3.0	1

exists as (82%) free chlorine and as (18%) hypochlorous acid; whereas at pH 8, 21% exists as hypochlorous acid and 79% as hypochlorite.

Hypohalites are converted into halates according to the following equations:

$$HOX + OX^- \longrightarrow HXO_2 + X^- \qquad (15)$$

$$HXO_2 + OX^- \longrightarrow HXO_3 + X^- \qquad (16)$$

As mentioned in Section I, disproportionation occurs most rapidly at a pH corresponding to the pK_a value [Eq. (*12*)]. The velocity of formation of halate increases greatly in the order $ClO_3^- < BrO_3^- < IO_3^-$; this order correlates directly with the leaving-group tendencies of the respective halide ion (see Table I).

a. Oxidation in Acidic and Neutral Solutions.—In acidic solution, the active oxidant is normally the free halogen molecule (for chlorine or bromine systems), and the hypohalous acid is less effective; this may derive from the relative stabilities of the anionic products of the oxidation, as the halogen, X_2, has two potentially good leaving-groups [see Eq. (*10*)], whereas the acid HOX has only one such group. The order of effectiveness as an oxidant, however, is in the order $Br_2 > Cl_2 > I_2$, the last being very ineffective. This order corresponds neither to the oxidation potentials (Table I) nor to the order of leaving groups; it does, however, correspond to the higher solubility and the rate of hydrolysis of the free halogen by water (k in Table I).

As already mentioned, the relative proportions of free halogen and hypohalous acid vary with the acidity of the solution and the nature of the halogen; however, unless a buffer or neutralizing compound is present, the solution becomes strongly acidic as a result of the formation of hydrohalic acid during the oxidation of an organic substrate [see Eqs. (*17*) and (*18*)].

$$RCHO + Br_2 + H_2O \longrightarrow RCO_2H + 2\,HBr \qquad (17)$$

$$RCHO + HOBr \longrightarrow RCO_2H + HBr \qquad (18)$$

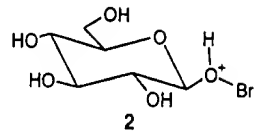
As described in Ref. 1 (pp. 1108, 1109), the first reports on the use of halogens for the oxidation of sugars to aldonic acids appeared by the end of the 19th century. The accumulation of hydrogen bromide during oxidations by bromine profoundly decreases the rate of further oxidation. This effect results from the increase in acidity and also may be due to complexation of free bromine as Br_3^-, which is ineffective as an oxidant. To minimize this inhibiting influence, the reaction may be conducted in the presence of a solid buffer, such as barium carbonate or calcium benzoate. In general, the presence of a buffer increases the yield of aldonic acid, and, in addition, it precludes the hydrolysis of disaccharides. Yields of 96% of D-gluconic acid and of 90% of D-xylonic acid (as salts) have been obtained from oxidation of the respective aldoses in buffered solutions. When the oxidation period is extended, particularly under unbuffered conditions, keto acids may be formed in low yields. Under more-drastic conditions, carbon–carbon bonds are cleaved, to yield chain-shortened acids.

A variation of the bromine oxidation process is the electrolytic oxidation of sugars in the presence of a bromide, and a solid buffer, such as calcium carbonate. The electrolytic reactions of sugars have been reviewed.[19] Presumably, the reaction occurs because of the formation of free bromine at the anode; the bromine oxidizes the aldose to the aldonic acid and is itself reduced to bromide. Yields are almost theoretical in many cases. If the electrolytic method is not well controlled, aldaric acids and 2- and 5-glyculosonic acids may be produced. Studies on the anodic oxidation of glucose using bromide and hypobromite ions as redox mediator have been conducted.[20] Such studies revealed that the rate of oxidation is independent of the glucose concentration but it is significantly affected by the interfacial mass transfer and the initial concentration of mediator. The electrolytic oxidation of lactose to yield calcium lactobionate has been optimized.[21] The process uses rotating graphite anodes, stationary graphite cathodes, and NaBr solution to electrogenerate Br^-/BrO^-. The continuous electrochemical oxidation of D-glucose yielded 94% conversion into sodium gluconate using a filtering anode made from carbon fibers and an optimun concentration of NaBr, buffered at pH 9, as electrolyte.[22] Other electrochemical oxidations of carbohydrates are described in the preceding chapter.

Ketoses are generally resistant to the action of bromine,[1] and bromine oxidation is sometimes used to remove aldoses from such mixtures as invert sugar. By extending the period of oxidation and employing high temperatures, degradation products are obtained from 2-ketoses. Under milder conditions the oxidation of ketoses leads to 5-hexulosonic acids. Calcium D-*arabino*-2-hexulosonate yielded 65% of calcium D-arabinonate by electrolytic oxidation with bromine.[19] For bromine oxidations of polyols, more-drastic conditions are needed than for aldoses. Cyclitols are also oxidized by the action of bromine in a buffered solution.[23]

Methyl α- and β-pyranosides of galactose, glucose, and mannose have been oxidized by bromine at neutral pH. Oxidation of secondary hydroxyl groups afforded 2-, 3-, or 4-uloses. A low degree of oxidation of the primary alcohols was also reported, although the initial products are rapidly converted into uronic acids.[24] Similarly, nonreducing disaccharides, α and β cyclodextrins (cyclomaltohexa- and heptaoses) and their derivatives have been oxidized by aqueous bromine solution at pH 7. Both ketone and carboxylic acid-containing materials are among the products of the oxidation.[25] A pH dependence for the reaction of bromine with cyclodextrin shows that the maximum rate of bromine loss roughly coincides with the maximum concentration of HOBr, indicating that this is the reactive species in these oxidations. A mechanism was suggested involving the attack of HOBr to one of the secondary HO groups of cyclodextrin, with Br^- leaving to yield an intermediate dehydroxy hydroperoxy cyclodextrin that subsequently decomposes to a keto-cyclodextrin. An alternative pathway prevails when the reaction is carried out under alkaline conditions, where carboxylic acids are the main products.

b. Mechanism of Bromine Oxidation of Aldoses.—Free bromine is the active oxidant of aldoses when they are treated with bromine in the presence of barium carbonate and bromides (pH about 5.4). Similarly, molecular chlorine was found to be the active oxidant in the oxidation of D-glucose by buffered chlorine–water at pH 2.2 and 3.[1] Interestingly, it is the cyclic forms of an aldose, and not the acyclic free aldehyde form, which are oxidized directly under these conditions. Pyranoses afford 1,5-lactones, and furanoses, 1,4-lactones, in high yield. The anomerically equilibrated solutions are oxidized at rates intermediate between those for the individual anomers, and the oxidation curve is composed of a rapid phase followed by a slow one. A detailed discussion on the kinetics of this type of oxidation has been given in Ref. 1, pp. 1110–1112. It is important to point out that the rate of bromine oxidation observed for α-D anomers suggests a dependence of the rates of mutarotation into the β-D anomers, and that the true rates of oxidation of the α-D anomers are much lower. Thus, the rate-determining



2

SCHEME 2

step in the oxidation of the α-D anomers is anomerization to generate the faster-reacting β-D anomer. For D-glucose, the true rate of oxidation of the α anomer was found to be about 1/250th that of the β anomer. It has been suggested that the higher rate of oxidation of β-D-glucopyranose is due to the equatorial orientation of the hydroxyl group on C-1; this group is less hindered for reaction with the bromine molecule, to give a cationic intermediate (**2**). Also its structure is stereoelectronically favored, as the positive charge is located on the anomeric substituent, which has the β configuration (reverse anomeric effect[26]). This intermediate undergoes conversion into D-glucono-1,5-lactone, via a hypobromous ester (see Ref. 1, pp. 1111–1114). However, Isbell[27] proposed an alternative explanation based on the difference in free energy between the respective ground and (presumed) transition states of the two anomeric anions derived from D-glucopyranose. The transition states are assumed to be similar in structure for both anomers; however, the transition state for the β-D anomer suffers less destabilization by nonbonded interactions (Scheme 2).

The increase in the rate of oxidation of aldoses with increase in pH from 1.25 to 4.5 was attributed to the progressively enhanced extent of participation by the anion of the aldose, which undergoes oxidation faster than the neutral aldose;[28] however, this implies a difference in reactivity of about 10^{11} and such an extreme difference in rate could not be explained by a difference in acidity only. Furthermore, relative rates of oxidation by bromine decrease in the order: β-L-arabinose > β-D-galactose > β-D-glucose > β-D-mannose, which precisely reverses the order of the extents of dissociation of these aldoses. Whereas the foregoing reactions of aldoses involve a free hydroxyl group at C-1, alkyl β-D-glucosides are also more readily oxidized by acidic chlorine, and also by alkaline hypochlorite, than the α-D-glucosides. As no hypohalite ester can be formed directly at the anomeric carbon atom, the relationship of oxidizability of the sugar to the acidity of the anion is not straightforward.

c. Oxidation of Aldopyranosides with Acidic Chlorine Systems.—Oxidation of methyl D-glucopyranosides with saturated chlorine–water (unbuffered, pH~1 initially) affords D-gluconic acid as main product, which is oxidized further to D-*xylo*-2-hexulosonic acid and D-glucaric acid.

In Ref. 1 (pp. 1114–1115) the effect of the axial or equatorial orientation of the aglycon in the rate of oxidation of a number of β-D-glycopyranosides is described. When the aglycon adopts an equatorial orientation [a β anomer in the $^4C_1$(D) conformation] the oxidation takes place at a higher rate (two to ten times) than for the α anomer. In the case of methyl L-arabinopyranosides, the α-L anomer, which, in the $^1C_4$(L) conformation has an equatorially attached group at C-1, is oxidized more rapidly.

Chlorine oxidation of methyl β-D-glucopyranoside to D-gluconic acid is very slow (50% conversion after 14 days at room temperature). The D-glucoside is, apparently, oxidized directly to D-gluconic acid, without initial hydrolysis of the glycosidic linkage. The oxidation of methyl β-D-glucopyranoside was conducted at several pH values; the major products formed at pH 4 were D-gluconic, D-erythronic, and glyoxylic acids; minor products were D-glucose, D-arabinose, and hexopyranosiduloses. Hypochlorous acid was considered to be the oxidant, based on the observations that the concentration of this species is maximum at pH 4 and that the yield of neutral products from the oxidation was also at a maximum at this pH value.[1]

d. Oxidation with Hypohalites in Alkaline Solution.—In alkaline solution, the halogens are converted into hypohalous acid and hypohalite ions. Hypohalite oxidation is likely to be more drastic than action of the free halogens. Thus, whereas free iodine does not act as an oxidant, hypoiodite is a powerful oxidizing agent. Hypobromite and hypochlorite, in particular, are prone to oxidize primary and secondary alcoholic groups, and to cause cleavage of carbon–carbon bonds; these processes are complicated by the tendency of hypohalites to disproportionate to halate ions [see Eqs. (*15*) and (*16*)].

The action of chlorine in alkaline media is much slower than that of bromine. Lewin[29] reported that the rate of oxidation of D-glucose at pH 9.8 by hypobromite is 1360 times higher than that by hypochlorite at the same pH. For cellulose, the ratio is much smaller (33 to 1). The complexity of the latter system is, however, revealed by the variability of this ratio over the pH range of 8–13; at pH 6–7, the action of hypochlorite is actually slightly faster than that of hypobromite. Maltodextrins and starch have been oxidized with alkaline sodium hypochlorite. The resulting oxidized polysaccharide formed stable complexes with calcium cations.[30]

Maximal rates of oxidation of sugars by chlorine and bromine have been observed near neutrality and several studies have been conducted in order to establish the identity of the active oxidant as well as the mechanism of the reaction (Ref. 1, pp. 1116, 1117). As for other related oxidations with halogens, β anomers of glycosides react more rapidly than the α anomer

with hypochlorite at pH 9 and 11. Similarly, the oxidation of β-D-glucopyranose by hypoiodous acid at pH 9.8 is, initially, at least 25 times as fast as that of the α anomer. As the oxidation progresses, the simultaneous mutarotation tends to equalize the two rates.

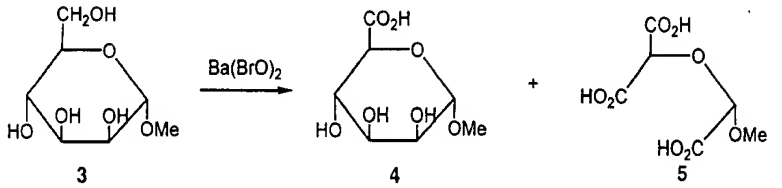
Alkaline hypoiodite oxidizes aldoses, under carefully controlled conditions, almost quantitatively to aldonic acids (see preceding chapter). Measurement of the iodine consumed permits quantitation of the amount of aldose originally present [Eq. (*19*)].

$$RCHO + I_2 + 3\,NaOH \longrightarrow RCO_2Na + 2\,NaI + 2\,H_2O \qquad (19)$$

The rate of the competitive reaction, namely the formation of iodate, should be lower than the oxidation of the aldose. Iodide ion suppresses iodate formation; however, too much iodide causes overoxidation by maintaining a higher concentration of oxidant (hypoiodous acid) during the reaction. Hypoiodite has been suggested as the reagent of choice for oxidizing fragments from periodate-oxidized polysaccharides to aldaric and lower acids for separation and identification.[31] Kinetic studies on the oxidation of hexoses and pentoses by iodine in alkaline solution have been reported.[32] The results indicated that the active oxidizing species is hypoiodous acid. Maximal oxidation is found at pH 11.2. A mechanism for the oxidation was proposed.

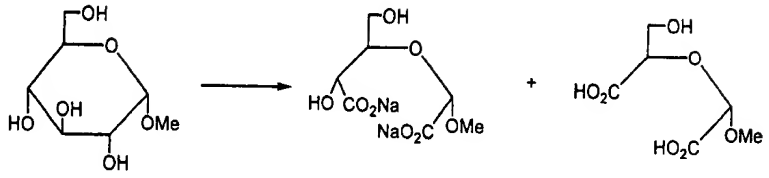
As previously reported (Ref. 1, pp. 1118, 1119) ketoses are essentially inert to the action of hypoiodites under the conditions used for the determination of aldoses, and aldosides are converted by hypoiodite or hypobromite into glycosiduronic acids in rather low yield. For example, methyl α-D-mannopyranoside (**3**) afforded methyl α-D-mannopyranosiduronic acid (**4**), although cleavage of carbon–carbon bonds also occurred to give **5** (Scheme 3).

Alditols are oxidized by alkaline solutions of some halogens, and the main product seems to be the 1,2-dicarbonyl derivative. However, in further studies on the oxidation of pentitols and hexitols with bromine in the presence of calcium carbonate, 2- and 3-uloses and 2,5-hexodiuloses were



3 4 5

SCHEME 3



SCHEME 4

identified by gas chromatography–mass spectrometry of the trifluoroacetylated *O*-methyloxime and *O*-butyloxime derivatives.[33,34]

Aldonamides having free hydroxyl groups at C-2 are degraded to the aldose having one less carbon atom by treatment with hypochlorites. This is the basis of the Weerman method of degrading aldoses (see Ref. 1, Chapter 3).

Suspended nickel peroxide seems to be the reactive species in the nickel-catalyzed oxidative cleavage of glycals, using sodium hypochlorite as the primary oxidant.[35] β-Cyclodextrin (cyclomaltoheptaose) was oxidatively cleaved (~ 50%) between C-2 and C-3, although oxidation at C-6 (~ 25%) appeared to occur as well. In contrast, maltodextrin (malto-oligosaccharides) was oxidized at the primary HO function, and methyl α-D-glucopyranoside (**6**) gave the diacid **7**, which was further degraded to **8** (Scheme 4).

2. Halic Acids (HXO_3)

In the presence of a small amount of bromide, acidic bromate oxidations are autocatalytic, and several oxybromo species are present in the reaction mixture,[36] according to Eqs. (*20*)–(*22*).

$$BrO_3^- + Br^- + 2H^+ \rightleftharpoons HBrO_2 + HOBr \qquad (20)$$

$$HBrO_2 + Br^- + H^+ \rightleftharpoons 2\,HBrO \qquad (21)$$

$$2\,HBrO_2 \rightleftharpoons H^+ + BrO_3^- + HOBr \qquad (22)$$

Bromous acid disproportionates rapidly, and at high bromate and acid concentration, a fast equilibrium is established between bromate and hypobromous acid [Eq. (*23*)].

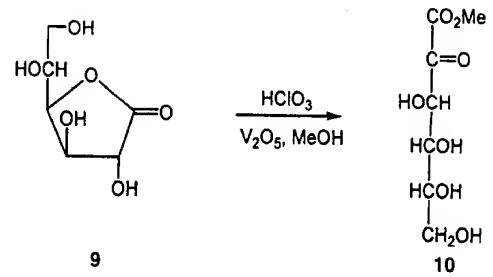
$$BrO_3^- + 2\,Br^- + 3\,H^+ \rightleftharpoons 3\,HBrO \qquad (23)$$

Under these conditions, oxidation by hypobromous acid predominates and autocatalysis is observed with organic substrates. Hypobromous acid oxidizes the substrate and is reduced to bromide, which promotes bromate decomposition. The only role of bromate is to reoxidize the bromide formed in the oxidative step.[36]

Acidic chlorate oxidations are also carried out with a small amount of chloride, and according to the reaction conditions, different equilibria predominate.[37] With these reaction systems, the oxidizing oxyhalogen species, formed *in situ*, promotes the oxidation of the primary alcohol groups of polysaccharides to carboxylic acids.[36] Thus, the stoichiometry of the overall oxidation in strongly acidic medium (85% H_3PO_4) is given by Eq. (*24*).

$$3\,RCH_2OH + 2\,HXO_3 \rightleftharpoons 3\,RCO_2H + 2\,HX + 3\,H_2O \qquad (24)$$

Chloric acid, in conjunction with catalysts (particularly vanadium pentaoxide), is used for the oxidation of aldonic acids or lactones to the 2-glyculosonic acids. Thus, D-glucono-1,4-lactone (**9**) and potassium D-galactonate in methanol, in the presence of phosphoric acid and vanadium pentaoxide, are oxidized by chloric acid to methyl D-*arabino*-2-hexulosonate (**10**) and methyl D-*lyxo*-2-hexulosonate, respectively.[38] At moderate temperatures in the absence of a catalyst, aldoses, ketoses, and sucrose are inert to the action of chlorates over a several weeks time period;[39] bromates in alkaline solution also exert no oxidative action (Scheme 5).



SCHEME 5

3. Chlorous Acid ($HClO_2$)

Chlorous acid is of particular interest because of its use for the removal of lignin and other noncarbohydrate components from woody tissue without

appreciable action on the carbohydrates (see Ref. 1, Chapter 37). It is also reported to be an effective bleaching agent.

Jeanes and Isbell[39] found that, under mild conditions, aldoses are oxidized to aldonic acids, but that nonreducing carbohydrates and ketoses are oxidized only slowly. The rate of oxidation decreases in the order: pentoses > hexoses > disaccharides; however, in contrast to other oxidants, chlorous acid oxidizes α-hexoses more rapidly than the β anomers. The yields of aldonic acids are, however, less than those from bromine oxidations.[40] The equation for the oxidation in acidic solution was expressed as:

$$RCHO + 3\,HClO_2 \longrightarrow RCO_2H + HCl + 2\,ClO_2 + H_2O \qquad (25)$$

The quantitative stoichiometry of the D-glucose–chlorous acid reaction has been studied in detail; the reagent used was sodium chlorite in a phosphoric acid–phosphate buffer at pH 2.4–3.4. The molar ratio of oxidant consumed to D-glucose consumed was 3:1; no overoxidation occurred over extended periods of time. The method is recommended for the determination of aldehyde groups in carbohydrates, especially alkali-sensitive carbohydrates.

The effectiveness of various chlorine oxidants, and the influence of the pH, on D-galacturonic acid has been studied (see Ref. 1, p. 1120). The autocatalytic chlorite oxidation of polysaccharides is similar to that described for the bromate oxidation (see Section II.2). Thus, the reactive oxyhalogen species are reduced to halides, as shown in Eq. (*26*).

$$RCH_2OH + HClO_2 \longrightarrow RCO_2H + HCl + H_2O \qquad (26)$$

4. Miscellaneous Halogen Oxidants: *N*-Halosulfonamides and *N*-Halosuccinimides

Whistler and co-workers[41] used chlorine in nonaqueous solvents (acetic acid or carbon tetrachloride) to effect chlorinolysis of glycosides. The initial products of this reaction are a glycosyl chloride and a hypochlorous ester [Eq. (*27*)].

$$GlOCH_2R + Cl_2 \longrightarrow GlCl + RCH_2OCl \qquad (27)$$

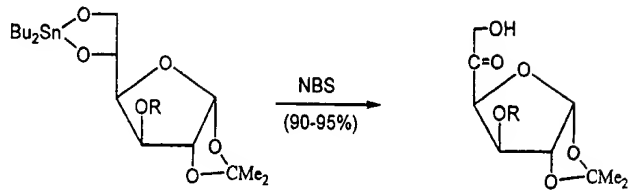
The presence of the glycosyl chloride was demonstrated by its conversion into an ethyl glycoside by ethanol in the presence of a silver salt. The hypochlorite ester formed by chlorinolysis of a methyl glycoside underwent

elimination of hydrogen chloride to give formaldehyde. A similar reaction with amylose produces the chlorinolysis of the $1 \rightarrow 4$ links and oxidation of the alcohol group on C-4, via a D-glucose-4-hypochlorite residue. The position of oxidation was proved by sequential reduction and hydrolysis of the product, to generate derivatives of both D-glucose and D-galactose. This reaction is an exception to the generalization that halogens as oxidants do not normally introduce halogen atoms into the compound.

Aromatic *N*-halosulfonamides are a group of mild oxidizing agents which contain the strongly polarized *N*-linked halogens in the +1 state. They undergo a two-electron change to form halide ions and the corresponding sulfonamides. Prominent members of this class of oxidants are *N*-chloro- and *N*-bromo-*p*-toluenesulfonamides (chloramine-T and bromamide-T, respectively). Oxidation of alcohol groups by NBS or *N*-bromoacetamide in acidic medium has been ascribed[42] to the oxidative attack of H_2BrO^+ species according to Eq. (*28*). A radical mechanism has also been proposed for the oxidative cleavage of 1,2-diols by *N*-halosuccinimides.[43] *N*-Bromosuccinimide (NBS), as well as *N*-bromoacetamide or *N*-bromocarbamide, in methanol, oxidize benzylated sugars to the corresponding aldonolactones.[44]

$$R_2CHOH + H_2BrO^+ \rightleftharpoons R_2CHO + 2\,H^+ + Br^- + H_2O \qquad (28)$$

Dibutylstannylene acetals of diols (such as **11**) were found to be oxidized regiospecifically by NBS to α-hydroxyketones (**12**)[45] (Scheme 6).



11 R = Me or Bn **12**

SCHEME 6

The ruthenium-catalyzed oxidation of aldoses by NBS under acidic[46] and basic[47] conditions have been investigated. The order of reactivity of some pentoses and hexoses has been determined for their oxidation by NBS in aqueous acidic media containing Hg(II) acetate. A mechanism for the reaction has been suggested on the basis of kinetic measurements.[48]

The oxidation of some hexoses[49] and pentoses[50] by *N*-chloroarylsulfonamides in alkaline conditions has been conducted, and the kinetics studied. The products were identified as the corresponding aldonic acids for aldoses, and arabinonic acid for fructose. Further studies[51] indicated that both

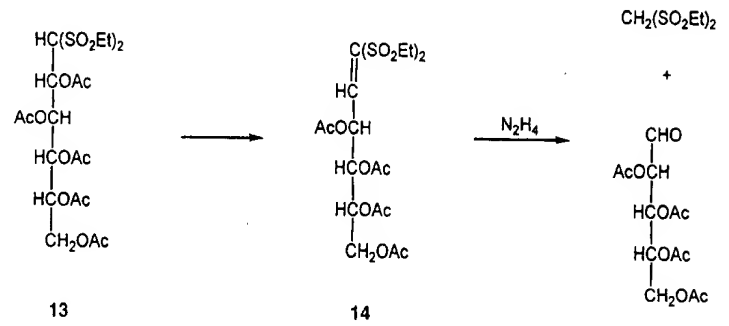
pentoses and hexoses of the *erythro*-series undergo oxidation to a mixture of aldonic acids: arabinonic, ribonic, erythronic, and glyceric. In the case of hexoses, oxidation occurs mainly with the cleavage of the C-1–C-2 and C-3–C-4 bonds, whereas pentoses are oxidized mainly with cleavage of the C-1–H and C-1–C-2 bonds. Based on these data, a mechanism involving the *aldo*-enolic anions of pentoses and *keto*-enolic anions of hexoses has been proposed.

Kinetics of oxidation of four pentoses by bromamide-T were conducted in alkaline medium at different temperatures and the overall activation parameters have been calculated.[52] Aldonic acids were the oxidation products, and a mechanism was suggested in which formation of the enediol anion of the sugar is the rate-limiting step. As aldoses may undergo epimerization in alkaline solutions, the oxidation of monosaccharides with bromamide-T was also performed in hydrochloric acid solution.[53] Kinetic parameters revealed a low reactivity of ketoses relative to aldoses, and indicated that the cyclic forms of the latter are involved in the oxidations.

III. Organic Peroxy Acids

Peroxy acids, RCO_2OH, are comparable to hypohalous acids, HOX, in that they possess a good leaving group, RCO_2^-, and so can develop an electrophilic center, HO^+ in the transition state [Eq. (*10*), $X = RCO_2^-$]. Such oxidants are either used as such, or are prepared as needed by the direct addition of hydrogen peroxide to the organic acid in the reaction mixture. Peroxy acids can react with alkanes to give hydroxylated products.[54] This may be an electrophilic reaction, because the rate increases with increased acidity of the peroxy acid. Dioxiranes are also able to insert an oxygen atom into alkanes.[55]

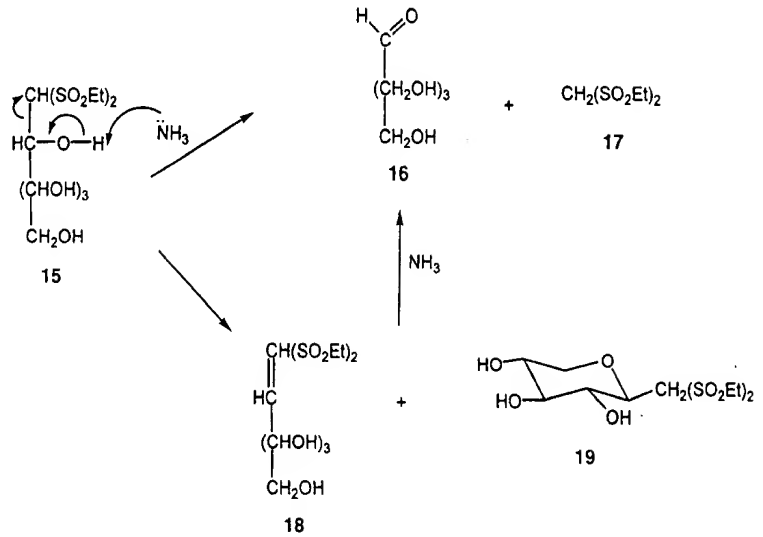
Peroxy acids, as an alternative to permanganate for the oxidation of aldose diethyl dithioacetals to disulfones, were first employed by MacDonald and co-workers.[56] Thus, D-glucose diethyl dithioacetal pentaacetate (**13**) was oxidized by peroxyphthalic acid in ether to 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1,1-bis(ethylsulfonyl)-D-*arabino*-hex-1-enitol (**14**); this unsaturated disulfone may be cleaved at the double bond by hydrazine to afford arabinose and bis(ethylsulfonyl)methane (Scheme 7). D-Lyxose was similarly prepared. Unacetylated aldose dithioacetals can be converted by the action of aqueous peroxypropanoic acid into disulfone derivatives, which are readily degraded in aqueous ammonia to the corresponding aldose having one fewer carbon atom.[57] D-Erythrose, D-threose, and D-arabinose were obtained in high yields from the dithioacetals of D-arabinose, D-xylose, and D-mannose. The ring in *scyllo-myo*-inosose was broken by oxidation of the dithioacetal and subsequent ammonolysis of both carbon–carbon bonds to



SCHEME 7

the sulfonylated center, affording *xylo*-pentodialdose. D-Fructose diethyl dithioacetal reacts with peroxypropanoic acid in 1,4-dioxane to afford a (presumably unstable) disulfone which decomposes spontaneously, yielding D-erythrose in a single step.

Hough and Richardson[58] explored the reaction of unacetylated hexose dithioacetals with peroxypropanoic acid; the sulfone **15** initially formed is only marginally stable, and undergoes dehydration to mixtures of the unsaturated disulfone (**18**) and the 2,6-anhydro-1-deoxy-1,1-bis(ethylsulfonyl)alditol (**19**). All three products are degraded by aqueous ammonia to the next lower sugar (**16**) and bis(ethylsulfonyl)methane (**17**). This degradation is much slower for **18** than for **15**, and it was concluded that hydration of **18** to **15** precedes disproportionation (Scheme 8).

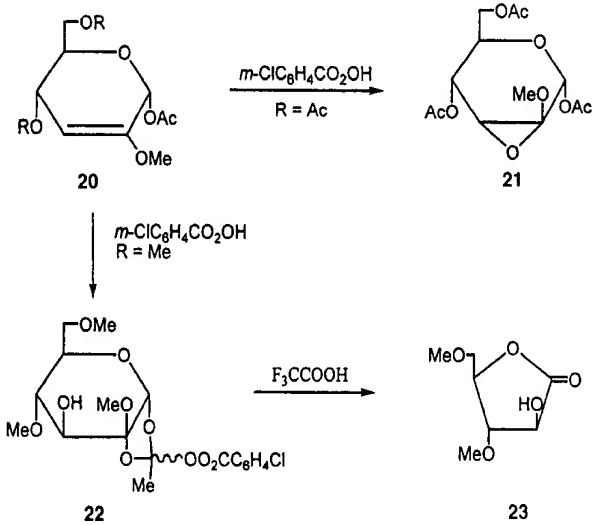


SCHEME 8

The cyclodehydration of **18** to the anhydroalditol derivative **19** has been explained as an attack by the 6-hydroxyl group on the double bond. Studies by Hall *et al.*[59] of acyclic sulfones formed from two heptose dithioacetals epimeric at C-2 revealed their ready conversion in hot water into a common 2,6-anhydride, which was shown by nuclear magnetic resonance (NMR) analysis to have the bulky bis(ethylsulfonyl)methyl group in the equatorial orientation. The sulfone prepared from D-arabinose diethyl dithioacetal cyclizes to 2,5-anhydro-1-deoxy-1,1-bis(ethylsulfonyl)-D-ribitol.[60] Horton and Norris reported[61] on a range of synthetic applications of dithioacetals and their oxidation products.

Although peroxy acids as reagents in sugar chemistry have been confined largely to oxidations of dithioacetals, they have also been used in the hydroxylation of alkenes to give dihydroxy derivatives. Such hydroxylation is normally *anti*; the initial epoxide, formed by *syn* addition to the double bond, suffers inversion of stereochemistry in the course of hydrolysis, to generate ultimately an *anti*-glycol grouping.

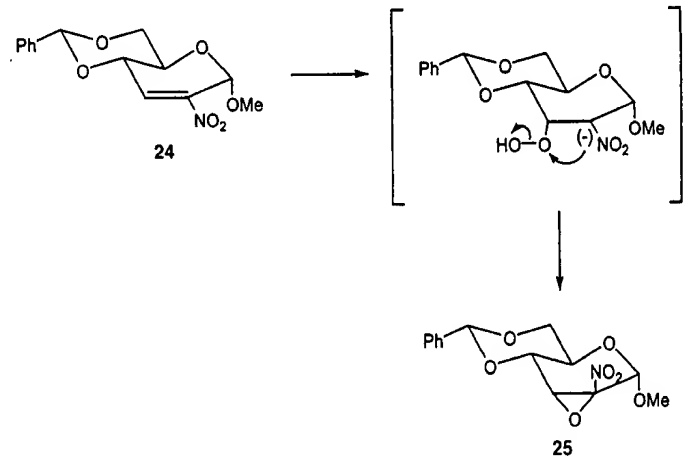
Aspinall and King[62] used *m*-chloroperoxybenzoic acid to epoxidize 1,4,6-tri-*O*-acetyl-3-deoxy-2-*O*-methyl-α-D-*erythro*-hex-2-enopyranose (**20**, R = Ac) to the corresponding oxirane **21**, which underwent hydrolysis to afford a hexopyranos-2-ulose derivative as the main product. 1-*O*-Acetyl-3-deoxy-2,4,6-tri-*O*-methyl-α-D-*erythro*-hex-2-enopyranose (**20**, R = Me) reacts with *m*-chloroperoxybenzoic acid to give the mixed orthoperoxy anhydride **22**, which decomposes spontaneously, in the presence of trifluoroacetic acid, to 3,5-di-*O*-methyl-D-arabinonolactone (**23**) (Scheme 9).



20 **21** **22** **23**

SCHEME 9

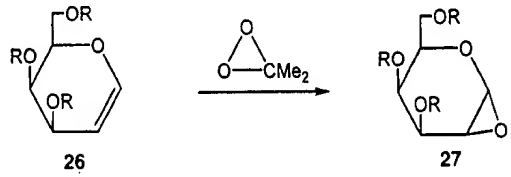
Stable epoxides of α,β-unsaturated carbonyl and nitro compounds have been obtained. For example, compound **24** reacts with hydrogen peroxide or alkyl hydroperoxides in the presence of a base to give **25**.[63] The reaction is believed to proceed by Michael addition of the hydroperoxide anion to **24**, and subsequent intramolecular displacement of hydroxide by the anion of the carbon atom that bears the nitro group (Scheme 10).



24 **25**

SCHEME 10

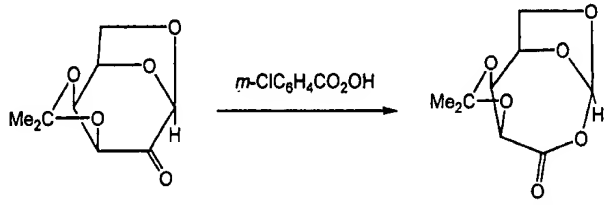
Oxidation of glycals with peroxy acids does not lead to isolable epoxides, as the initially formed 1,2-anhydro sugar reacts with the acid derived from reduction of the peroxy acid. However, direct epoxidation of glycals (such as **26**) to 1,2-anhydro sugars (**27**) has been achieved with anhydrous 3,3-dimethyldioxirane.[64] The byproduct, acetone, does not react with the 1,2-epoxide. Similarly, perfluoro-*cis*-2,3-dialkyloxaziridines effect direct epoxidation of the tri-*O*-acetyl derivatives of D-glucal and D-galactal, and di-*O*-acetyl-L-rhamnal, to give neatly the corresponding 1,2-anhydro sugars with moderate to complete diastereoselection.[65] Glycals and hex-4-enopyranosides have also been stereoselectively epoxidized with a *m*-chloroperoxybenzoic acid–potassium fluoride complex[66] (Scheme 11).



26 **27**

SCHEME 11

The Baeyer–Villiger transformation of several protected derivatives having a free ketone group has been effected by *m*-chloroperoxybenzoic acid. Thus, 1,6-anhydro-3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-2-ulose (**28**) was converted into the cyclic, orthoacid anhydride **29**.[67] As an additional example, the Baeyer–Villiger oxidation of Ferrier carbocyclization products derived from D-glucose afforded 5-deoxyhexofuranosiduronic acids, via the ring-expanded lactonic intermediates[68] (Scheme 12).



28 **29**

SCHEME 12

IV. PHENYLHYDRAZINE AS AN OXIDANT

Under controlled, acidic conditions, an excess of phenylhydrazine acts specifically to convert the (usually terminal) –CO–CHOH– grouping in aldoses or ketoses into a bis(phenylhydrazone) residue, which undergoes ready hydrolysis to liberate a –CO–CO– grouping. Simultaneously, reductive cleavage of the nitrogen–nitrogen bond of the oxidant gives aniline and ammonia as products. As the applications of phenylhydrazine as a net oxidant have been described in detail in the second edition of "The Carbohydrates" (Ref. 1, pp. 1125, 1126) and also several aspects on the chemistry of bis(phenylhydrazones) are treated in the preceding chapter and in Chapter 21 of Ref. 1, no further discussion on this subject is included here.

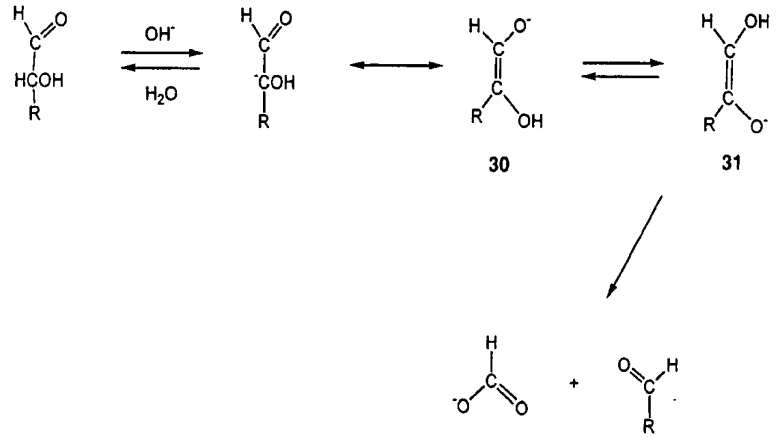
V. OXYGEN IN ALKALINE AND NEUTRAL SOLUTION

Study of the action of molecular oxygen on sugars is of considerable interest insofar as it relates to the mechanism of the *in vivo* oxidation of sugars; the influence of configurational and conformational features on the course of catalytic oxidations is an intensively studied topic. Molecular oxygen has synthetic utility for the degradation of sugars to acids having

shorter chains. The catalytic oxidation of carbohydrates and related compounds by oxygen and hydrogen peroxide has been recently reviewed.[69]

1. Oxidation in Alkaline Solution

In alkaline solution, oxygen degrades aldoses to aldonic acids having one fewer carbon atom. Air or oxygen may be used, and relatively high yields of acids are obtained.[70] Ketoses act similarly; oxidation of L-sorbose affords L-*xylo*-2-hexulosonic acid plus L-xylonic acid in good yield. The formation of the reaction products has been rationalized by assuming ionization of the aldoses or ketoses to intermediate enediols (**30**, **31**) by the action of the base, followed by the radical or ionic addition of oxygen. The intermediate 2-glyculosonic acid gives the next lower aldonic acid by decarboxylation (Scheme 13).



30 **31**

SCHEME 13

3-*O*-(α-D-Glucopyranosyl)-D-arabinonic acid and its β anomer were prepared by oxidation of maltose and cellobiose, respectively;[71] 3-*O*-(β-D-galactopyranosyl)-D-arabinonic acid is formed similarly from lactose.

In its ground state, the oxygen molecule exists as a diradical; it is a stable molecule in isolation, and its reactivity is greatly enhanced in the presence of catalysts. In alkali-catalyzed autooxidation, fragmentation of carbon–hydrogen bonds is either caused or greatly facilitated by alkali; subsequent transfers of electrons are relatively rapid and facile processes.

The reaction of oxygen with cellulose in alkali (autooxidation or alkaline aging) was interpreted as being a free-radical process (see Ref. 1, p. 1127) initiated by loss, from an activated molecule (for instance, an enol), of a

labile hydrogen atom, followed by capture of oxygen by the radical to generate a hydroperoxy radical. Abstraction of a hydrogen atom from the substrate (RH) would afford the radical R·, which is propagated in a chain reaction. The hydroperoxides formed can decompose in various ways to give an oxidation product, or to produce oxy radicals that can react with molecules of RH, thus accelerating its oxidation.

For the oxidative degradation of D-glucose, Bamford and Collins[72] proposed that oxygen adds to the enediol anion, forming a hydroperoxide intermediate that decomposes to arabinonic and formic acids. However, the direct combination of the carbanion with oxygen is considered to be a highly improbable initiation process; Russell[73] pointed out that such a step would require bond creation and a change in multiplicity (a spin-forbidden process). Similarly, an ionic mechanism based on hydride transfer from a doubly-ionized aldehydrol group, and subsequent attack by a hydroperoxyl anion, incorporates a step similar to the one disputed by Russell.

Gersmann *et al.*[74] suggested another mode of initiation, which proceeds by deprotonation of RH to a carbanion that transfers one electron to an oxygen molecule; capture of oxygen produces a peroxy radical that oxidizes another molecule of the initial carbanion, the last two steps constituting a chain-propagation process. In hydrocarbon oxidations, Russell[73] also showed that reactions of carbanions with O_2 proceed via a two-step one-electron transfer pathway [Eqs. (*29*)–(*32*)].

$$RH + OH^- \longrightarrow R^- + H_2O \qquad (29)$$

$$R^- + O_2 \longrightarrow R^\bullet + O_2^{\bullet-} \qquad (30)$$

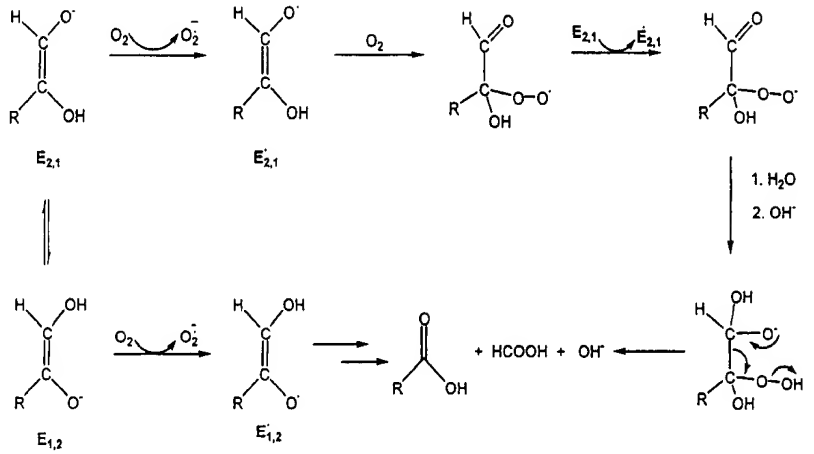
$$R^\bullet + O_2 \longrightarrow ROO^\bullet \qquad (31)$$

$$ROO^\bullet + R^- \longrightarrow ROO^- + R^\bullet \qquad (32)$$

Further studies verified the intermediate formation of free radicals, as demonstrated by the electron-spin resonance spectra obtained during autooxidation of cellulose,[75] and hydrogen peroxide was identified as a byproduct in the autooxidation of D-glucitol. Similar oxidations of cellulose in the presence of alkenic monomers afforded graft copolymers. The autooxidation of cellulose and of the cello-oligosaccharides was shown to be more extensive in the presence of transition-metal cations.

Vuorinen[76] demonstrated by $^{17}O_2$ labeling experiments that cleavage of the enediol anion proceeded via the C-1 and C-2 hydroperoxides in a 1:2

ratio. Sheldon *et al.*[69] suggested a general mechanism for the oxidation of aldoses in alkaline media that takes into account the rapid equilibrium between the enediolates $\mathbf{E_{1,2}}$ and $\mathbf{E_{2,1}}$. This equilibrium was combined with the Russell mechanism of reaction with O_2 to form peroxy-radicals, which in consecutive steps underwent cleavage. This mechanism does not require a spin-forbidden addition of triplet oxygen to the enediol anion (Scheme 14).



SCHEME 14

The formation of monohydroxy acids having chains of four, three, or two carbons can be rationalized with the same mechanism of oxidation of the corresponding enediol. The 1,2-enediol can rearrange to the 2,3- or 3,4-enolates, which undergo the oxidative cleavage. Alternatively, the enediol may undergo a retro-aldol condensation followed by oxidation.

Although these alkali-catalyzed oxidative degradations are interesting from the mechanistic point of view, they cannot be controlled and hence, they do not find preparative use.

2. Catalytic Oxidation

In the presence of platinum catalysts, the main process effected on sugars by oxygen is dehydrogenation.[77] Isotopic oxygen is not incorporated into the organic product, and the dehydrogenation is not reversible in the presence of $H_2{}^{18}O$. The oxidation seems to be a radical process, with initial

attack on a C–H bond [Eq. (*4*)]; the stability of the resulting radical is the important factor [Eq. (*5*)]. As with platinum, such related metals as palladium and rhodium are effective catalysts for oxidation of alcohols. Such oxidations in the carbohydrate field have been reviewed.[69,77]

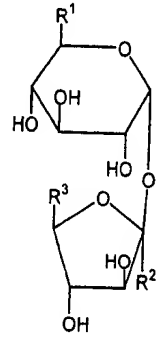
As the catalytic oxidation occurs on a catalyst surface, it is profoundly influenced by steric effects: (a) oxidation of the anomeric position of aldoses takes place selectively to give the corresponding aldonic acids; (b) when the anomeric position is protected, as in glycosides, or it has been reduced to an alditol, primary alcoholic groups are generally oxidized rather than secondary alcoholic groups; (c) when only secondary hydroxyl groups on a pyranoid ring are available, the favored attack is on a carbon atom bearing an axially attached hydroxyl group; and (d) in the case of rigid, bicyclic molecules, the favored attack is on the carbon atom bearing an *endo* hydroxyl group.

Platinum-catalyzed oxidation of D-glucitol affords L-gulose and D-glucose. The specificity of this reaction is probably due to both statistical and steric factors. A related example is the conversion of L-sorbose into L-*xylo*-2-hexulosonic acid in 62% yield (see Ref. 1, p. 1129). Similar oxidation of 1,2-acetals of α-D-glucofuranose and α-D-xylofuranose affords the respective glycuronic acids whereas, under more drastic conditions, the former acetal is converted into 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulosono-6,3-lactone, a synthetic precursor of ascorbic acids.

This method of oxidation has been extensively used in the preparation of alkyl and aryl glycopyranosiduronic acids,[77] and it has also been applied to the oxidation of other glycopyranosides, aldopentofuranosides, disaccharides, and polysaccharides. Also, several examples have been given[1] showing that the oxidation of axially attached secondary alcoholic groups occurs preferentially when primary alcoholic groups are either absent or protected. In correlation with the attack on the equatorially attached hydrogen atoms of the (axial) alcohol groups, several glycoside derivatives have been oxidized. Similarly, oxidation of a series of partially protected acetals of ketoses revealed that primary hydroxyl groups react faster than axial secondary hydroxyl groups, that proximity to the ketogenic center slows the reaction of the former more than the latter, and that equatorial secondary hydroxyl groups are almost inert. The favored oxidation of axial hydroxyl groups was also demonstrated for anhydro sugars and anhydrohexitols. The Pt–C-catalyzed oxidation of 1,4;3,6-anhydro-D-glucitol in aqueous solution brought about conversion of both free hydroxyl groups into carbonyl functions.[78]

The oxidation of D-glucose 1-phosphate and analogues to the alduronic acid 1-phosphates by molecular oxygen over Pt on carbon occurred with

oxidation of secondary HO groups and subsequent C–C bond cleavage as side reactions. These side reactions are retarded by substituents at C-5, and the protecting ability follows the order CO_2^- > CH_2OH > H.[79] The Pt–C-promoted oxidation of sucrose by oxygen at 100 °C and neutral pH proceeded with high selectivity for the oxidation of HO-6 and HO-6′, with no evidence for reaction at HO-1.[80,81] Oxidation of sucrose by an alternative procedure, in oxygen-saturated aqueous solution, with the pH adjusted by addition of $NaCO_3H$, led to sucrose monocarboxylic acids with a selectivity of 96%. The three primary CH_2OH groups are converted in a 10:9:1 ratio [C-6 fructose (**32**), C-6′ glucose (**33**), C-1 fructose (**34**)], correlating with the accessibility of each group to the Pt surface[82] (Scheme 15). Methyl α-D-fructofuranoside was oxidized with O_2–Pt (C), at 60 °C and pH 9, to methyl α-D-*arabino*-hex-2-ulofuranosiduronic acid, with 83% selectivity. Oxidation of inulin under the same conditions led to only partially oxidized products (20% of the primary hydroxyl groups). Adsorption and desorption phenomena appear to play an important role during the oxidation process.[83]



32 $R^1 = R^2 = CH_2OH$, $R^3 = CO_2H$

33 $R^1 = CO_2H$, $R^2 = R^3 = CH_2OH$

34 $R^1 = R^3 = CH_2OH$, $R^2 = CO_2H$

SCHEME 15

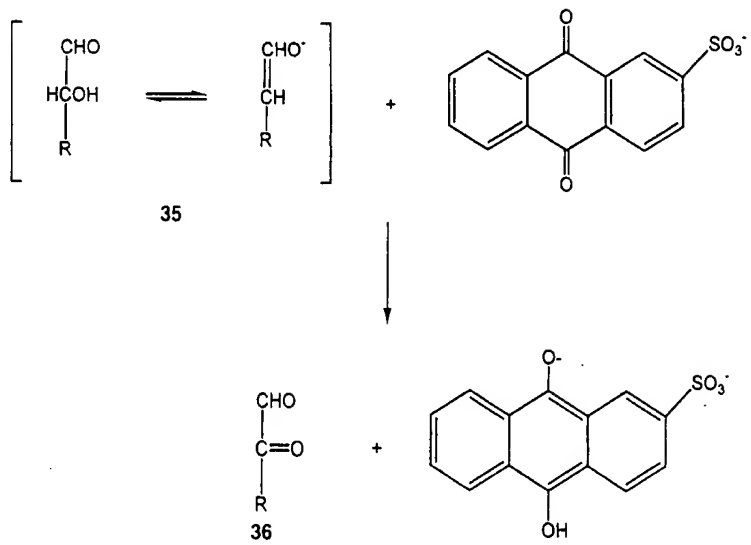
As with platinum, the palladium-catalyzed oxidation of anomeric hydroxyl groups in aldoses is a rather selective process.[84] The influence of pH in the Pd-catalyzed oxidation of glucose has been studied. It was observed that the gluconic acid formed, in its free form, reversibly inhibits the oxidation process in acidic media.[85] The oxidation of D-glucose has been performed with palladium-on-alumina and with bismuth-containing palladium-on-charcoal in water.[85] The selectivity in the air oxidation of

aqueous D-glucose and D-gluconate has also been examined, with Pt catalysts supported on activated charcoal, with or without such promoters as bismuth or gold. The combined use of such heavy metals as bismuth, together with Pt or Pd, introduced an important improvement in the selectivity of these catalytic oxidations. Thus, the use of Pd, or both Pd and Pt catalysts, doped with bismuth,[86–88] led to an enhancement in the selectivity of the oxidation. An additional advantage of these catalysts is that their susceptibility to poisoning by molecular oxygen is strongly diminished, making the oxidations more efficient. These processes are useful for the oxidation of D-glucose and various mono-, di-, and oligo-saccharides on the industrial scale.

The oxidation of secondary hydroxyl functions to the carbonyl group is often an undesired side reaction. However, the oxidation of D-gluconic acid to "2-oxogluconic" acid is a highly selective process (97% yield) when a Pt–Bi catalyst is employed.[89] Such a procedure is of industrial interest.

The so-called pyrochlore oxides are mixed metal oxides which have high surface areas. They have been prepared as combinations of ruthenium–bismuth and ruthenium–lead.[90] Exposure of methyl α-D-glucopyranose in aqueous solution (0.7 *M* KOH) at 50–75 °C to oxygen at 10–20 bar in the presence of bismuth-rich ruthenium pyrochlore oxide caused glycol cleavage to give the C-2,C-4-dicarboxylate with the concomitant formation of formate. On prolonged reaction, the primary hydroxyl group was also oxidized to carboxylate.[91] Cyclomaltoheptaose (β-cyclodextrin) reacted nonselectively, and the catalyst does not seem to be suitable for the controlled oxidation of starch.[92]

The kinetics have been studied of the alkali-catalyzed oxidation of D-glucose with sodium anthraquinone-2-sulfonate in aqueous ethanol. At high concentration of the quinone, the rate-determining step for the oxidation is the enolization of D-glucose, to give the intermediate **35** and hence "D-glucosone" (D-*arabino*-hexos-2-ulose, **36**) as the primary product[93] (Scheme 16). The quinone is a better acceptor than oxygen of a single electron from the enediol. The resulting radical, itself or combined with O_2 via a peroxide, gives the aldosulose. This product is not further oxidized by the quinone, but if H_2O_2 is added, oxidative degradation of the glycosulose to the aldonic acid and formate takes place. Thus, lactose is degraded by this procedure to β-D-galactopyranosyl-(1 → 3)-D-arabinonate in 90–95% yield, whereas the classical oxidative degradation with O_2 in alkali gives the same product in only 75–80% yield. A mechanism for the highly selective oxidative degradation of carbohydrates by sodium anthraquinone-2-sulfonate and H_2O_2 (Spengler–Pfannenstiel oxidation) has been proposed[94].



SCHEME 16

3. Oxidation Under Neutral Conditions

Under conditions simulating biological processes (neutral, aqueous solutions at a temperature of 37.5 °C), oxygen attacks D-glucose, glyceraldehyde, glycerol, and related polyols. One mole of carbon dioxide is formed per mole of D-glucose; sodium ferropyrophosphate has been used as the catalyst. D-Fructose is much more sensitive than D-glucose in the presence of phosphate or arsenate as the catalyst, and the rate of oxidation depends on the concentration of salt present. The action of oxygen on disaccharides and polysaccharides, as well as some aspects of the mechanism of these oxidations has been previously reported (Ref. 1, p. 1131). Further studies have shown that the oxidation of D-xylose, D-glucose, D-glucitol, cellulose, and dextran by oxygen at 170–230 °C affords relatively high yields of acetic and formic acids; increased yields were obtained by addition of iron(II) sulfate as catalyst.[95]

The aqueous oxidation of D-[1-^{14}C]glucose and D-[6-^{14}C]glucose at 100 °C afforded formic, acetic, and glycolic acids, and carbon dioxide. The last is mainly produced from C-2 to C-5, the formic acid from C-1, and the acetic acid from C-6.[96] Addition of aluminum(III) chloride greatly increased the yield of carbon dioxide. Oxidation of D-glucose and D-fructose, studied with ^{18}O-enriched oxygen, showed that they decompose via the C-1 and C-2 hydroperoxides to give D-erythronic acid as the main product.[76]

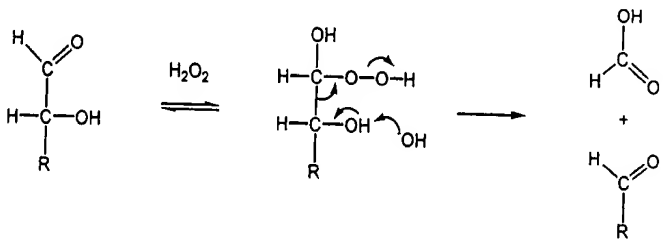
VI. Hydrogen Peroxide

Hydrogen peroxide is an ineffective oxidant in polar solvents at acidic or neutral pH, as the formation of a hydroperoxide ion is quite difficult [Eq. (33)]. When the pH is increased, the equilibrium that exists in neutral H_2O_2 solutions is shifted to the right [Eq. (*34*)].

$$HOOH \rightleftharpoons H^+ + HOO^- \qquad (33)$$

$$HOOH + HO^- \rightleftharpoons HOO^- + H_2O \qquad (34)$$

In alkaline solutions, hydrogen peroxide is used as a bleaching agent; its initial action on cellulose and on amylopectin[97] is depolymerization. Oxidation seems to occur mainly on reducing end-units and other partially oxidized positions; the (strongly nucleophilic) hydroperoxide anion is more likely to attack the polarized carbonyl than alcohol groups (see Scheme 17). Isbell and co-workers showed that alkaline peroxide degrades aldoses,[98] ketoses,[99] and reducing disaccharides[100] sequentially to formic acid, by a series of enolization and oxidation processes. Together with glycuronic and glyculosonic acids, oxalic acid and also formic acid are obtained as products.[101] Hydroperoxide intermediates have been proposed in the oxidation of methyl β-D-glucopyranoside.[102]

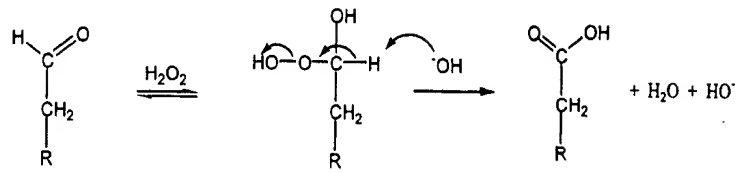


Scheme 17

In the case of 2-deoxyaldoses, where no hydroxyl group is present at C-2, the α-hydroxy-hydroxyperoxide cleavage is not possible and a different pathway affords the 2-deoxyaldonic acids,[103] as shown in Scheme 18.

Many other degradation mechanisms (which are not described here) have been proposed by Isbell and Frush[104] in order to account for the various oxidation products formed from carbohydrates by the action of H_2O_2.

Since traces of heavy metals and metal ions catalyze the decomposition of H_2O_2 into water and oxygen, stabilizers can be added to the solution of H_2O_2. Such chelating agents as EDTA, are effective for the stabilization of H_2O_2. Thus, the degradation of aldoses by aqueous alkaline H_2O_2 was



Scheme 18

rendered much more selective upon addition of EDTA, in the presence or absence of borate ions. Under these conditions galactose, lactose, maltose, and cellobiose were each converted into the next lower aldoses and formic acid, in high yield.[105]

The effect of borate is to form esters with hydroxyl groups of the carbohydrates, which impedes degradation during the oxidation. In this reaction it is essential for the HO groups at C-2 and C-3 to be in *threo* relationship.[105,106] In contrast to the classical oxidative degradation of lactose, protection against overoxidation by borate results in a good yield (>70%) of "galarose." Likewise, cellobiose, maltose, and galactose were succesfully degraded to the next lower aldoses in the presence of borate ions.[107]

Use of catalysts, generally ferric or ferrous salts, promotes radical reactions with hydrogen peroxide; the oxidizing action produced by the ferrous ions is more vigorous.

1. Hydrogen Peroxide and Ferric Ions

Ferric ion catalyzes the formation of the hydroperoxyl radical, according to Eq. (*35*); such a radical appears to constitute the oxidant in the Ruff method of degrading aldonic acids to the next lower aldoses. A number of examples of the use of this reagent in the laboratory are given in a review article by Moody.[108] The hydroperoxyl radical, which is not so effective an oxidant as the hydroxyl radical, does not attack aliphatic alcohols: accordingly, a substantial yield (about 50%) of the aldose is obtained from the higher aldonic acid. In the presence of an excess of hydrogen peroxide, however, the accumulation of ferrous ions in solution catalyzes the production of hydroxyl radicals and lowers the yield of aldose [see Eq. (*36*)].

$$Fe^{3+} + HOOH \longrightarrow Fe^{2+} + H^+ + {}^{\bullet}OOH \qquad (35)$$

A possible mechanism for this reaction suggests the formation of a carboxyl radical, which undergoes degradation to liberate CO_2. The resulting radical produces the corresponding next lower aldose plus H·.

Hydrogen peroxide in acetonitrile has been shown to convert a pentofuranosidulose oxime into the corresponding nitro derivative.[109]

2. Hydrogen Peroxide and Ferrous Ions

The Fenton reagent is a mixture of hydrogen peroxide and a ferrous salt, which leads to the formation of hydroxyl radicals, according to Eqs. (*36*)–(*40*). Hydroxyl radicals are very effective in abstracting hydrogen atoms, in contrast to the weaker action ascribed (Section VI.1) to hydroperoxyl radicals.

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^{\cdot} + HO^{-} \quad (36)$$

$$Fe^{2+} + HO^{\cdot} \longrightarrow Fe^{3+} + HO^{-} \quad (37)$$

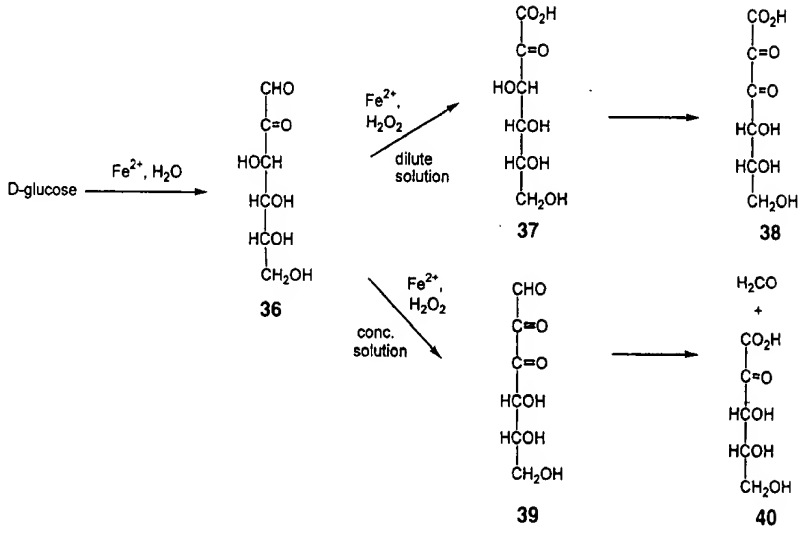
$$H_2O_2 + HO^{\cdot} \longrightarrow H_2O + HO_2^{\cdot} \quad (38)$$

$$Fe^{2+} + HO_2^{\cdot} \longrightarrow Fe^{3+} + HO_2^{-} \quad (39)$$

$$Fe^{2+} + HO_2^{\cdot} \longrightarrow Fe^{2+} + O_2 + H^{+} \quad (40)$$

Studies by electron-spin resonance spectroscopy showed that the reaction of hydroxy radicals with carbohydrates produces new radicals via hydrogen abstraction from a C–H group. When such carbohydrates as glucose are substrates, the H· abstraction from a C–H bond is relatively nonselective, and all six possible radicals can be formed. The fate of these radicals is strongly influenced by the type of starting sugar and by the species present in the reaction medium. All of these aspects have been discussed in the review article by Sheldon *et al.*[69]

At low temperatures, D-glucose and D-fructose in the presence of ferrous sulfate are converted into D-*arabino*-hexos-2-ulose (**36**), which can be degraded by further oxidation to glycolic acid, glyoxylic acid, and D-erythronic acid. The nature of the products formed under various conditions and the mechanism of the reaction have been described (see Ref. 1, p. 1133). In dilute solution, in the presence of ferrous sulfate at low temperature, compound **36** gave D-*arabino*-2-hexulosonic acid (**37**) and D-*erythro*-hexo-2,3-diulosonic acid (**38**). In concentrated solutions, formaldehyde was also found. The formation of these products at low temperature was ascribed to the series of reactions in Scheme 19.



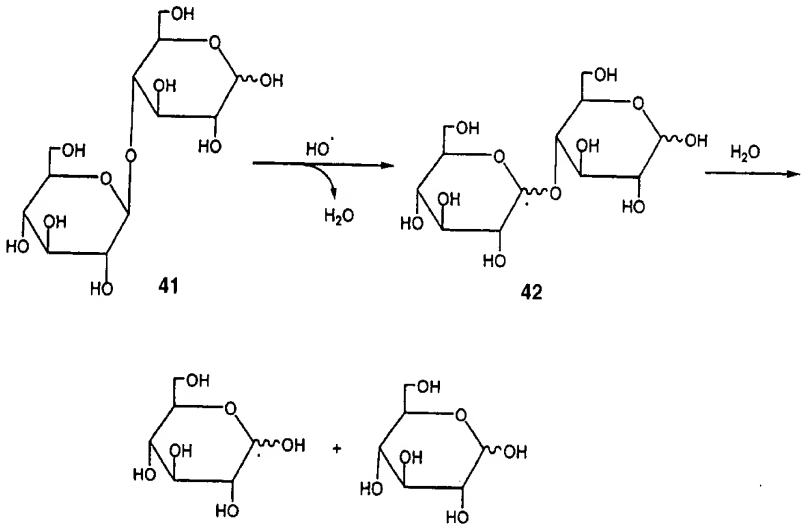
SCHEME 19

At higher temperatures, carbon dioxide, formic acid, oxalic acid, glycolic acid, hydroxymalonic acid, glyceric acid, and other acids were shown to be formed. The formation of carbon dioxide is ascribed to decarboxylation of **38**; oxalic acid and D-erythronic acid arise from cleavage of the C-2–C-3 bond; compound **39** is cleaved to glyoxylic acid plus D-erythronic acid. Compound **40** is oxidized further to D-*glycero*-2,3-pentodiulosonic acid and is subsequently cleaved to oxalic and glyceric acids.

The degradation of "2-deoxyribose" by Fenton's reagent has been conducted in acidic, neutral, and alkaline media, and in the presence and absence of hydroxyl-radical scavengers. It seems that both the substrate and the scavengers interact with the metal ions.[110] Traces of Fe(II) accelerate the oxidation of carbohydrates by H_2O_2, but larger quantities of such a cation has a retarding effect.[111]

Primary alcoholic groups are oxidized to aldehydes by the action of peroxide and ferrous ions. The action of the Fenton reagent on 3,4-di-*O*-methyl-D-mannitol gives (among other products) the products of demethylation, indicating that the hydroxyl radical attacks the C–O–Me grouping as well as primary alcoholic carbon atoms.[112] Oxidation of 1 mol of methyl β-D-glucopyranoside with 1.5 mol of hydrogen peroxide in the presence of ferrous ion gives small proportions of pyranosiduloses and D-glucose; undetermined amounts of D-erythronic and D-arabinonic lactones were also formed.[113] The products of degradation of cellobiose (**41**) under Fenton's conditions have been analyzed by liquid chromatography,

which showed that D-glucose and organic acids were the main products.[114] The formation of D-glucose could be due to the abstraction of hydrogen from the anomeric carbon of cellobiose (**41**) to give **42**, which underwent hydrolysis (Scheme 20).



SCHEME 20

VII. NITRIC ACID, NITROGEN DIOXIDE, AND NITROXYL RADICALS

Nitric acid is a strong acid and is a potent oxidant, but its salts are rather unreactive. Under strongly acidic conditions, it converts primary alcoholic and aldehydic groups into carboxylic acid groups. Frequently, however, cleavage of carbon–carbon bonds occurs. Conversion of D-galactose into (insoluble) galactaric ("*mucic*") acid occurs to the extent of > 70%, and the reaction may be used for the quantitative determination of this sugar.[115] Aldoses are oxidized by nitric acid to aldonic and aldaric acids or their lactones (see Ref. 1, pp. 1136, 1137). D-Glucose, for example, is oxidized by nitric acid to D-gluconic acid and D-glucaric acid. Alditols are oxidized to aldonic acids; oxidation of glycerol gives DL-glyceric acid. Aldonic acids are oxidized to 2-glyculosonic acids, aldaric acids, and glycuronic acids. Among the products of the oxidation of D-fructose are formic acid, oxalic acid, erythraric acid, and glycolic acid, but the reaction seems to require more severe conditions than for D-glucose; at low temperature, the ketoses are not attacked by 32% nitric acid.

Oxidation of methylated sugars with nitric acid was used extensively by early workers for locating the position of unsubstituted hydroxyl groups.[116] Cleavage of carbon–carbon bonds appears to be facilitated by the presence of such catalysts as vanadium salts. As hot nitric acid acts as a hydrolyzing agent as well as an oxidant, oligo- and poly-saccharides may be used directly.

The reaction probably proceeds via the cyclic forms of the sugars and lactones, as equilibria between the various cyclic forms and the acyclic form are presumably established rapidly under the strongly acidic conditions of these oxidations. Thus, D-galactose undergoes oxidation to (acyclic) galactaric acid, whereas similar reaction of D-mannose affords a dilactone (see preceding Chapter).

The specificity of the oxidation may be enhanced by the use of nitrogen dioxide (NO_2) instead of nitric acid.[117] In gaseous form, or in nonaqueous solution, this reagent exhibits a marked specificity for the oxidation of primary alcoholic (and aldehydic) groups; it converts glycosides into glycuronic acids, and cellulose into a D-glucuronan. Nitrogen dioxide has been recommended as an inexpensive oxidizing agent for the production of oxalic acid from carbohydrates.[118]

The oxidation and subsequent hydrolysis of starch to α-D-glucofurano-urono-6,3-lactone has been studied; nitric acid alone, or in combination with nitrites, and nitrogen dioxide, have been examined as oxidants. Good results were obtained for oxidations with nitric acid in the presence of formic acid. A number of patents have been issued on these topics (Ref. 1, pp. 1137, 1138). Treatment of methyl β-D-glucopyranoside with liquid nitrogen dioxide for 5 h at 12 °C afforded mostly D-glucaric acid, and three isomeric hexopyranosiduloses accounted for an additional 6% of the products.[119]

Concentrated nitric acid encounters an initial induction period as an oxidizing agent, and it exerts no oxidizing action in the presence of urea, which removes nitrous acid. The induction period is eliminated by the addition of fuming nitric acid, oxides of nitrogen, nitrous acid, or various other compounds.[115] Nitrogen dioxide requires the presence of water for its oxidizing action. These observations indicate that the true oxidant is not nitric acid, but that the effective agent is nitrous acid, which is formed in aqueous solutions of nitric acid or nitrogen dioxide according to the following equilibria:

$$HNO_3 + 2\,NO + H_2O \rightleftharpoons 3\,HNO_2 \qquad (41)$$

$$2\,NO_2 + H_2O \rightleftharpoons HNO_2 + HNO_3 \qquad (42)$$

Under conditions simultaneously favorable for these equilibria and unfavorable for carbon–carbon bond cleavage, the specificity of the reaction is greatly increased. Oxidation of primary alcohol groups appears to proceed through the intermediate formation of an ester of nitric (or nitrous) acid.

An improvement of the oxidation of polysaccharides by nitrogen oxides with respect to the degree of oxidation and the molar mass distribution of the products, can be made by dissolving the substrate in 85% phosphoric acid and adding an stoichiometric amount of sodium nitrite as oxidant.[120–122] The oxidizing nitrogen oxides are formed *in situ* from nitrite. However, the oxidation is not completely selective and some ketones are produced through oxidation of secondary hydroxyl groups.

An advantageous variant of the oxidation of polysaccharides by nitrogen oxides in 85% phosphoric acid consists in the use of sodium nitrate, instead of sodium nitrite, as the stoichiometric oxidant and a catalytic amount of sodium nitrite to decrease the induction time.[123] The advantage of this variant may be seen by taking into account the stoichiometry of the overall reactions:

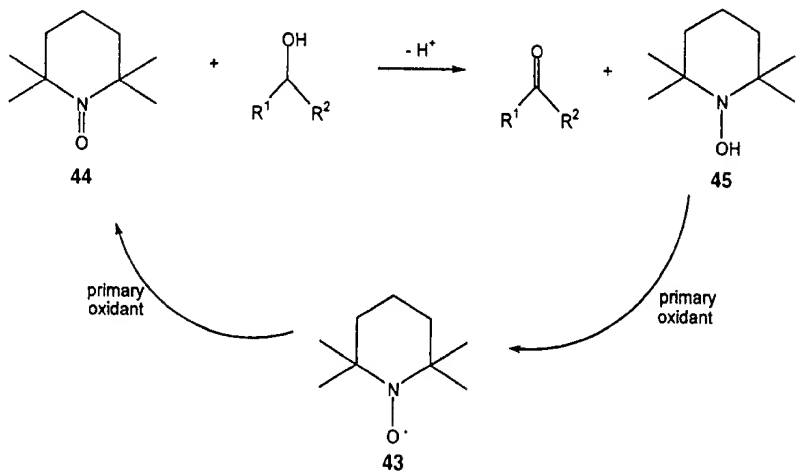
$$RCH_2OH + 4\,HNO_2 \longrightarrow RCO_2H + 4\,NO + 3\,H_2O \qquad (43)$$

$$3\,RCH_2OH + 4\,HNO_3 \longrightarrow 3\,RCO_2H + 4\,NO + 5\,H_2O \qquad (44)$$

For the oxidation of primary hydroxyl groups, three times the amount of nitrite is required when compared with nitrate, and three times as much of the toxic NO would be formed. This oxidation procedure has been applied to the glucans cellulose, amylose, and pullulan. A study of this system with cyclomaltoheptaose (β-cyclodextrin) showed that the reaction is autocatalytic.

Stable organic nitroxyl radicals are of relatively recent use as catalysts in the oxidation of alcohols. Nitroxyl radicals are compounds that contain the *N*,*N*-disubstituted NO-group with one unpaired electron, and their uses have been reviewed.[124] The most simple radical of this class is 2,2,6,6-tetramethylpiperidin-1-oxyl (**43**, TEMPO). It is generally assumed that the active oxidizing species, the oxoammonium salt (**44**), is formed in a catalytic cycle by a one-electron oxidation of the nitroxyl radical by a primary oxidant [two-electron oxidation of the hydroxylamine (**45**) is also possible, depending on the primary oxidant] (Scheme 21).

In the "classical" method, sodium bromide is needed to catalyze the formation of **44**, and other primary oxidants, mainly NaOCl, have been employed.[125] The TEMPO reagent has also been regenerated by



44 **45** **43**

SCHEME 21

electrochemical oxidation.[126] The system NaOCl–TEMPO has been efficiently used for the oxidation of partially protected or unprotected mono-, oligo-, and poly-saccharides.[125,127] The oxidation of sucrose by NaOCl–TEMPO, with or without the addition of NaBr as cocatalyst, is accelerated by sonication. The three primary groups of sucrose are oxidized to carboxylic acids.[127] The rate-controlling step of the reaction was found to be the oxidation of the primary hydroxyl groups by the nitrosonium ion. The chemoselective oxidation of primary alcohol groups of malto-oligosaccharides (maltodextrins) with the ternary oxidation system NaOCl–NaBr–TEMPO was shown to be strongly pH dependent.[128] Oxidation of polysaccharides is best achieved at pH 9.5 in order to minimize depolymerization, whereas oxidation of oligo- and mono-saccharides requires more strongly alkaline conditions. Thus, D-glucose was oxidized in high yield (>90%) to D-glucaric acid under strongly basic conditions (pH>11.5). In the absence of NaBr as cocatalyst, the oxidation of starch and methyl α-D-glucopyranoside required high temperatures.[129]

VIII. Chromium(VI)-Based Oxidants

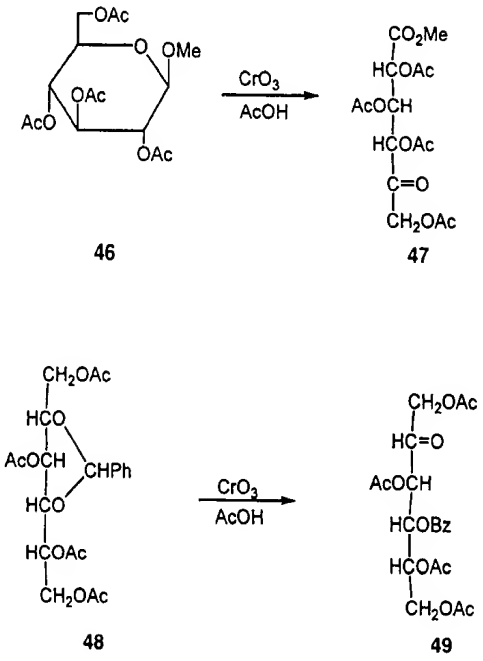
Oxides and oxyacids of Cr(VI) are powerful oxidants. The oxidative power of chromic acid is comparable to that of nitric acid. Chromic esters have been proposed as intermediates in these oxidations, thus isopropyl chromate has been isolated and converted into acetone by pyridine-catalyzed elimination in benzene solution [Eq. (*2*)]. Decomposition of the chromate ester involves removal of the proton attached to the

oxygen-bearing carbon. At least two mechanisms have been suggested for this step (see Ref. 10, p. 223) and an alternative proposal[7] involves the formation of a coordination complex that decomposes to radical species, which are further oxidized to products. Mechanistic studies are difficult because the oxidation of alcohols with Cr(VI) is a complex reaction that is influenced by the solvent, the acidity of the reaction medium, the structure of the alcohol, the temperature, and other factors.

Chromic acid (chromium trioxide) is a more generally useful oxidant than either nitric acid or permanganate, because it is stable in organic solvents. Oxidation of alcohols by chromic acid is much faster in acetic acid than in mineral acids of the same concentration; this higher rate has been ascribed either to the decrease in dielectric constant, which favors ester formation, or to formation of the more-reactive acetic chromic anhydride. *tert*-Butyl chromate has been used as an oxidant in acetic acid or in acetic acid–benzene; it acts by rapid transesterification to oxidize primary and secondary alcohols. Mixtures and complexes of chromium trioxide with pyridine have been used. Acetone, used as the reaction solvent, inhibits further oxidation of carbonyl-containing products and is, therefore, extremely useful. Various Cr(VI) oxidants have been employed in synthesis (see Ref. 10, pp. 221–234). Reagents prepared from chromic acid are efficient for the oxidation of isolated alcoholic groups in partially protected sugar derivatives. Pioneering work on Cr(VI) oxidations of sugar derivatives having free hydroxyl groups have been described in detail (Ref. 1, pp. 1139–1142). The properties of Cr(VI) and V(V) as oxidizing agents are also compared in Section XII.1.

The oxidizability of acetals was investigated by Angyal and James,[130] who found that acetylated methyl glycosides react with chromium trioxide–acetic acid to give acetylated methyl aldonates having a keto group in place of the oxygen atom formerly involved in the furanoid or pyranoid ring; methyl β-D-glucopyranoside tetraacetate (**46**) thus afforded methyl 2,3,4,6-tetra-*O*-acetyl-D-*xylo*-5-hexulosonate (**47**). Primary alkylidene acetals are opened to esters of ketoses by the same reagent[131] 1,3,5,6-tetra-*O*-acetyl-2-*O*-benzylidene-D-glucitol (**48**) is thus oxidized to a *keto*-D-fructose derivative (**49**). Primary alkyl groups as aglycons[132] or ether substituents[133] are similarly oxidized to acyloxy substituents (Scheme 22).

Oxidation of β-D-hexopyranosides by chromic acid is much faster than for their anomers,[130] and Hoffman *et al.*[134] have suggested the use of this reagent to cleave β-D-linkages selectively in heteropolysaccharides. The more-facile oxidation of the alcohol having the *endo* hydroxyl group was attributed to the relief of steric strain in the transition state as the trigonal carbonyl group is being formed, and to the unimolecular decomposition of the intermediate chromic ester through a cyclic transition-state that is



46 **47**

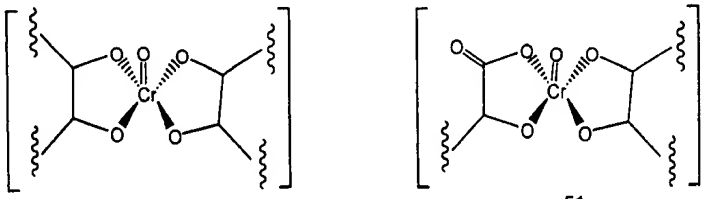
48 **49**

SCHEME 22

favored by the decrease in rotational freedom of the hindered ester. Steric factors may play an important role.[135] For example, 1-*O*-benzoyl-2,3:5,6-di-*O*-isopropylidenegalactitol undergoes ready oxidation at C-4 by chromic acid to afford the corresponding 3-hexulose derivative, whereas the stereoisomeric *manno*, *gulo*, and *allo* derivatives having a *cis* arrangement of the 1-*O*-benzoyl and 4-hydroxyl groups do not react with this reagent.

The chromic acid–pyridine complex oxidizes the free hydroxyl groups of carbohydrates to glyculoses. Horton *et al.*[136] reported good to fair yields for chromic acid–pyridine oxidations of a number of derivatives having an unprotected hydroxyl group in a primary or exocyclic secondary position, but endocyclic alcohol groups are generally less reactive. The basicity of pyridine can alter the stereochemistry of the product by epimerization of the carbon center α to the carbonyl group. Both pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) have been employed for the oxidation of sugar derivatives. For example, the 5-*O*-acylated derivatives of 1,4:3,6-dianhydro-D-glucitol and -D-mannitol gave the corresponding 2-keto derivatives in high yields.[137] Various reagents and procedures, including Swern oxidation, PDC, and tetra-*n*-propylammonium

tetraoxo-ruthenate(VII) with *N*-methylmorpholine *N*-oxide as cooxidant have been compared for the oxidation of aldose derivatives having the anomeric hydroxyl group free to the corresponding lactones.[138] The last of these reagents was very effective and afforded analytically pure lactones in 83–98% yield. The kinetics and synthetic aspects of the oxidation of sugars by PCC,[139] and the oxidation of aldoses and sugar phosphates by Cr(VI) have been reviewed.[140] Sala and co-workers studied the Cr(VI) oxidation of aldoses[141–143] and deoxyaldoses[141–145] in perchloric acid solution. For the 2-deoxy sugars, the lack of HO-2 accelerates the total reaction, and the HO-6 group may bind Cr(VI) as an intermediate ester. The kinetics of the reaction have been established by using an excess of sugar over Cr(VI). The redox reaction occurs through both Cr(VI) → Cr(III) and Cr(VI) → Cr(V) → Cr(III) pathways. Intermediate sugar alkoxide radicals may be trapped with 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and observed by electron paramagnetic resonance. These radicals react rapidily with Cr(VI) to form Cr(V). Such spectra showed that five- and six-coordinate oxochromate(V) intermediates are formed, with the aldose (**50**) or the aldonic acid (**51**) acting as bidentate ligands.[143] The oxidation of α- and β-D-glucose by Cr(VI) was conducted in dimethyl sulfoxide in the presence of pyridinium *p*-toluenesulfonate, a medium in which mutarotation is slower than the redox reaction. Both anomers reduce Cr(VI) by formation of an intermediate ester that is the precursor of the slow redox step. The equilibrium constant for the complex formation, and the rate of electron transfer within the complex, have been determined for each anomer. The equilibrium constant is higher for the α anomer, as the 1,2-*cis*-diolate moiety favors the Cr(VI) [or Cr(V)] chelation, and consequently, the activation barrier for the redox step is higher than that for the intermediate chelate formed from the β anomer. Because of the compensation of these two effects, the kinetic constants are of the same order for both anomers[146] (Scheme 23).



50 **51**

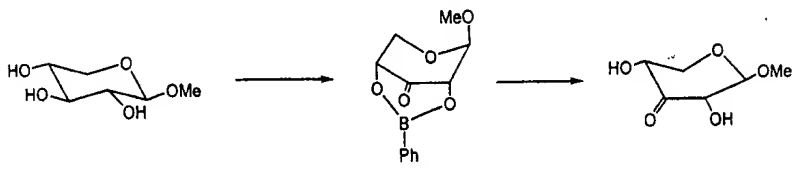
SCHEME 23

Investigation of a cellulose sample that had been oxidized by aqueous chromic acid in the presence of sulfuric acid showed that most

of the attack had occurred at C-3, as reduction and subsequent hydrolysis gave some D-allose, but no D-mannose.[147] The action of chromic acid on the 2-amino-2-deoxy analogue (chitosan) as the perchlorate (salt) was, however, directed almost exclusively to C-6 to afford an aminodeoxy-glycopyranuronan.[148]

IX. DIMETHYL SULFOXIDE

Pfitzner and Moffatt reported the use of methyl sulfoxide–*N*,*N*′-dicyclohexylcarboiimide as an oxidizing reagent.[149] It was subsequently shown that anhydrides, and also a variety of reagents in combination with methyl sulfoxide, effect oxidation of isolated hydroxyl groups. This oxidation method in organic chemistry has been reviewed,[150] and Jones and co-workers[151] presented a detailed comparison of the relative suitability of this and other oxidation methods for the oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose to the corresponding 6-aldehydo derivative. Primary hydroxyl groups in partially protected sugar derivatives tend to react faster, but a number of side reactions have been reported. For example, partially acylated derivatives commonly undergo elimination of a molecule of acid to generate a site of unsaturation conjugated with the newly formed carbonyl group.[152,153] Dimethyl sulfoxide-based oxidation of a number of sugar derivatives, and some side reactions that take place in individual cases, have been detailed in Ref. 1 (p. 1143). The Pfitzner–Moffat oxidation of isolated, secondary alcohol groups in otherwise protected molecules generally proceeds in good yield, whereas complicating side reactions are sometimes associated with similar reactions in the presence of more than one unprotected hydroxyl group. However, the difficulties that could be expected for the oxidation of unprotected methyl α- and β-D-xylopyranosides by this method are neatly avoided by the temporary introduction of a 2,4-cyclic phenylboronate protecting group prior to the oxidation; by this procedure, methyl β-D-xylopyranoside (**52**) was converted into methyl β-D-*erythro*-pentopyranosid-3-ulose (**54**) in 45% overall yield via the phenylboronate **53**[154] (Scheme 24). Successful



52 **53** **54**

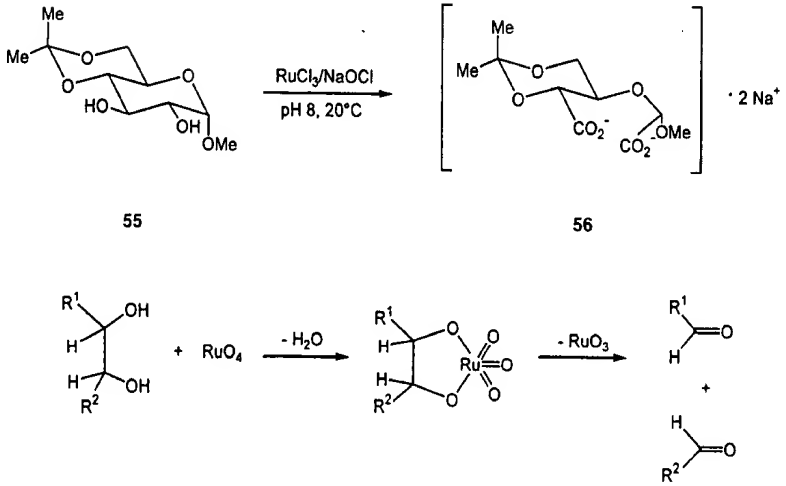
SCHEME 24

examples of selective oxidation of only one of several free hydroxyl groups of sugar derivatives and polysaccharides have been reported.[1]

X. Ruthenium Tetraoxide

Ruthenium tetraoxide is a powerful oxidant; it is more reactive than osmium tetraoxide, and combines explosively with ether or benzene, so that it is generally used as a dilute solution in carbon tetrachloride. Beynon *et al.*[155] first demonstrated the usefulness of this reagent in carbohydrate chemistry by converting methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*- and -D-*arabino*-hexopyranosides into methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose.

The oxidant may be prepared before the reaction in the stoichiometric amount needed, or be generated *in situ* by reaction of a catalytic amount of ruthenium dioxide with periodate[156,157] or hypochlorite.[158] Among a variety of oxidants studied, RuO_4 was found to be the best for the C-2–C-3 cleavage of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**55**) to the corresponding dicarboxylate **56**. In this case, RuO_4 was prepared *in situ* by oxidation of a catalytic amount of Ru(III) with sodium hypochlorite.[159] The presumed mechanism of the Ru-catalyzed diol cleavage is also shown in Scheme 25.



SCHEME 25

The catalytic method serves to minimize further oxidations, such as the Baeyer–Villiger reaction (see Section III); the latter reaction has been demonstrated to occur when the period of oxidation is extended.

The complex $Ru(tpy)(bpy)O_2^+$ [tpy = 2,2′,2″-terpyridine, bpy = 2,2′-bypyridine] oxidizes organic substrates by hydride abstraction or oxo transfer. This complex, and its derivatives, cleave DNA by oxidation of the sugar at the 1′ position and oxidation of guanine. Oxidation at the 1′ position leads to the release of free bases and a furanone product. The kinetic parameters for the oxidation of D-ribose, "2-deoxy-D-ribose," and nucleotides by $Ru(tpy)(bpy)O_2^+$ were determined in phosphate buffer (pH 7). The increased reactivity of DNA as compared to RNA was rationalized on the basis of deactivation of the sugar oxidation product by the polar effect of the 2′-hydroxyl group.[160]

Analytically pure lactones were obtained by oxidation of sugar derivatives, having the anomeric hydroxyl group free, with tetra-*n*-propylammonium tetraoxo-ruthenate(VII) and *N*-methylmorpholine *N*-oxide as cooxidant.[138]

The use of ruthenium tetraoxide as an oxidant in organic chemistry has been reviewed[161] and several applications to the carbohydrate field have been described (Ref. 1, p. 1147).

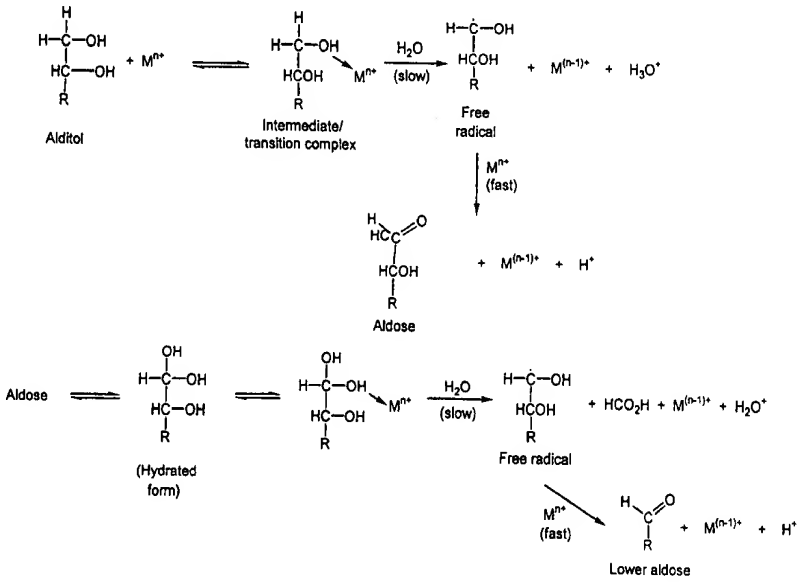
XI. Permanganate and Manganese Oxides

Permanganate is a powerful oxidizing agent, but there are other oxidation states available to manganese, including manganate and hypomanganate. Their oxidizing power varies inversely with the charge of the oxidant.[162] Primary and secondary alcohols are rapidly oxidized by alkaline permanganate; the reaction is slower in neutral and mildly acidic solutions. The rapid oxidation in alkaline solution has been attributed to the formation of a nucleophilic alkoxide anion. The choice of solvent is dictated by the type of protecting group used: acetates are oxidized in acetic acid, and isopropylidene acetals in alkaline solution. Unprotected glycol groupings and double bonds are usually attacked by alkaline permanganate, often resulting in carbon–carbon bond-cleavage. Under controlled conditions, permanganate (or osmium tetraoxide[163]) effects *cis*-hydroxylation of double bonds. Examples of oxidation of a number of sugar derivatives by the action of permanganate have been given (Ref. 1, p. 1147).

The relative reactivities and kinetic behavior of some aldoses, amino sugars, and methylated sugars toward permanganate in perchloric acid medium have been studied.[164] The oxidation of the hemiacetal to the corresponding lactone is facile; in agreement, the oxidation of methyl glucopyranoside is much slower than that of the parent glucose. Kinetics have been also performed for the permanganate oxidation of pentoses, hexoses, and ketoses in aqueous alkaline media.[165]

Manganese dioxide has been used to effect degradation of aldoses to the next lower aldoses.[166] Reducing disaccharides are converted into *O*-hexosylpentoses; further degradation to the *O*-hexosyltetrose is apparently obscured by oxidation of the tetrose residue to acidic products. Low yields of tetroses have been obtained from pentoses. Manganese dioxide has also been used for the oxidation of isolated alcohol groups of carbohydrates.[1]

Manganese(III) has been employed for the oxidation of aldoses, and a general mechanism for the oxidation has been proposed.[167] The oxidation of hexoses, pentoses, hexitols, and pentitols by Mn(III), as well as by other cations, was proposed to proceed via a free-radical mechanism,[168] as shown in Scheme 26. Oxidation of alditols produces the corresponding aldoses, which are further oxidized in the presence of an excess of oxidant to the lower monosaccharides and thence to formaldehyde, formic acid, and even carbon dioxide. The kinetics for the oxidation of aldoses and ketoses by Mn(III) in sulfuric acid medium have been reported.[169]



SCHEME 26

XII. MISCELLANEOUS OXIDANTS

1. Transition-Metal Cations

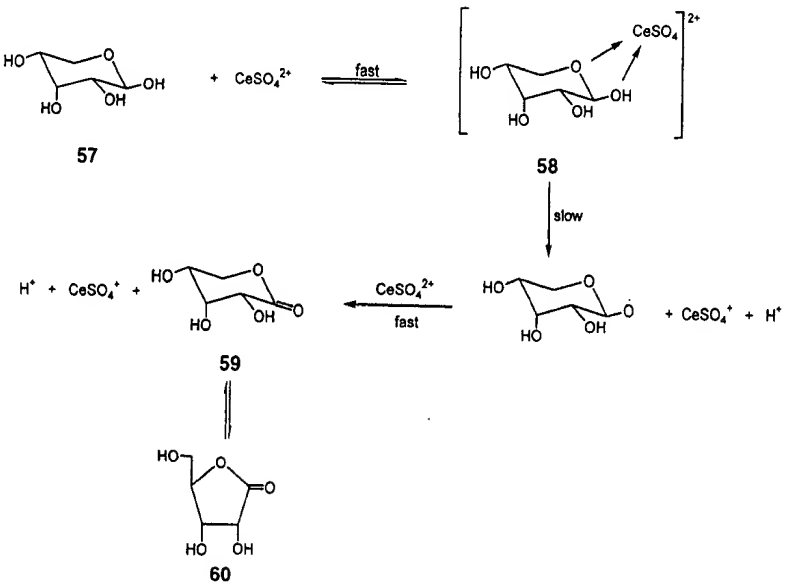
Oxidation of aldoses and ketoses with ferricyanide under alkaline conditions involves the 1,2-enediol as an intermediate. Such an oxidation has been previously described in detail (Ref. 1, p. 1148). A number of studies on the kinetics of oxidation of sugars with transition-metal cations (vanadium, cerium, thallium, and others) have been conducted during the past two decades. Such studies are briefly summarized in this section. A review[170] has been published on the metal-ion oxidations of reducing sugars.

Polyhydroxy compounds are oxidized by such metal ions as vanadium(V), chromium(VI), cerium(IV), iridium(IV), and gold(III), among others. These oxidations were found to be catalyzed by acids.[171–173] Vanadium(V) and chromium(VI) are closely related in their chemical properties, but the reduction of V(V) is difficult compared with that of Cr(VI) because of its lower redox potential [V(V)–V(IV) = 1.00 V; Cr(VI)–Cr(III) = 1.20 V]. However, the redox potential increases at lower pH values, facilitating the oxidation of sugars.

The hydroxyl groups of polyhydroxy compounds are readily esterified by vanadate, as demonstrated by ^{51}V NMR.[174] The kinetics of oxidation of pentoses and hexoses,[172] and D-erythrose and glyceraldehyde,[173] by vanadium(V) and chromium(VI) in perchloric acid was shown to be first order in oxidant and substrate. The reactions are catalyzed by acid, but their dependence on acidity is complex. The activation parameters were calculated and radical mechanisms, consistent with the experimental observations, were proposed. Thus, it was suggested that V(V) reacts with the hydrated aldoses to yield free-radical intermediates and VO^{2+}. The free radical is further oxidized by another $VO(OH)^{2+}$ cation in a fast step to give the products. The effect of pressure on the rates of oxidation of aldoses and ketoses by V(V) in perchloric acid has been investigated.[175] The negligible dependence in all of the cases on pressure up to 200 MPa was interpreted as demonstrating the formation of activated monosaccharide–vanadium complexes. It was suggested that, in the rate-determining decomposition of these complexes, hydrogen transfer takes place from the substrate to $V(OH)_2^{3+}$ to give a carbohydrate radical which undergoes rapid C–C or C–H bond fission. Oxidation is facilitated by a neighboring carbonyl group, which stabilizes the carbohydrate radical.[176] D-Fructose and L-sorbose give dicarbonyl compounds as primary products, and aldopentoses furnish aldotetroses. The reduction of V(V) and Mo(VI) in aqueous HCl by various hexoses, pentoses, ethylene glycol, and ethanolamine showed that the reducing abilities of these compounds are comparable with those of L-ascorbic acid and cysteine.[177]

Spectrophotometric studies on the kinetics of oxidation of some aldoses by Ce(IV) in sulfuric acid medium show that, as similar with oxidations with V(V), the reactions are first order with respect to the cation and aldose concentration. The formation of a radical as the rate-determining step has been proposed.[178] In fact, the oxidation of hexoses,

pentoses, hexitols, and pentitols by V(V), Ce(IV), Mn(III), and Tl(III) in aqueous acidic media have been claimed to proceed by a radical mechanism.[179] It has been shown that cyclic pyranoid forms (such as **58**), and not the aldehydo forms, of D-glucose and D-ribose (**57**) are involved in their oxidation with metal ions. The lactones (**59** and **60**) are the initial products of oxidation (Scheme 27).

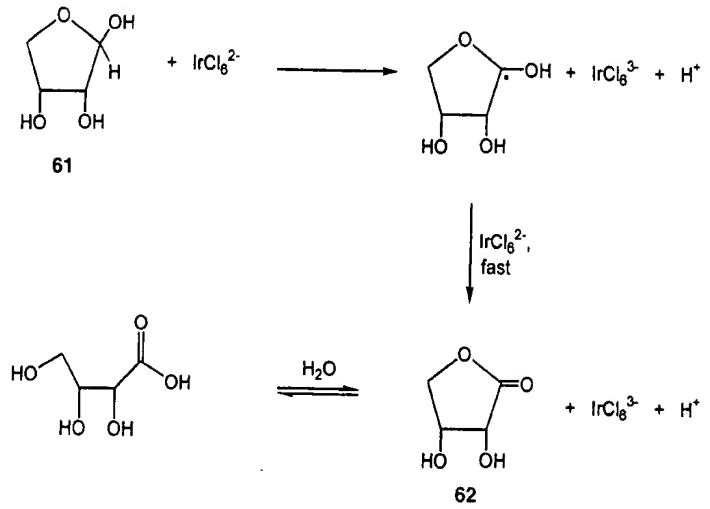


SCHEME 27

In perchloric acid, hexoses and pentoses are oxidized by Ce(IV) via formation of two complex intermediates. The first is partly oxidized following Michaelis–Menten kinetics and partly dissociated to the second, which is oxidized more slowly than the former.[180] The first step in the oxidation of aldoses by Tl(III) in the same medium involves the C-1–C-2 cleavage of the aldehydo form of the sugar. Thus, D-glucose gives D-arabinose and formic acid. With an excess of oxidant the final product is carbon dioxide.[181] In the presence of a catalytic amount of sulfuric acid in acetic acid, Tl(III) oxidizes maltose and lactose to the corresponding disaccharide aldonic acids. The reaction showed activation enthalpies and enthropies characteristic of second-order reactions.[182]

Many other cations of transition metals have been employed for the oxidation of sugars. For example, the oxidation of aldoses by hexachloroiridate(IV)[183,184] and tetrachloroaurate(III)[183,185] in hydrochloric acid led to the corresponding aldonic acids or aldonolactones. The observed

reaction orders respective to cation and substrate suggested the formation of a free-radical intermediate by fission of the anomeric C–H bond. Such a radical is then converted into the products. The oxidation of D-erythrose (**61**) by hexachloroiridate(IV) is shown in Scheme 28. The oxidation of D-glucose 6-phosphate by these two complex species was also studied.[186]



SCHEME 28

Most of the oxidations described in this section were performed in order to ascertain their mechanisms, but in general, they have not been employed for preparative purposes.

2. Copper(II) Oxide and Copper(II) Salts

The kinetics of oxidation by copper(II) in the presence of alkaline citrate and tartrate revealed that, as with ferricyanide, the rate of reaction is zero order in oxidant and directly proportional to the concentration of sugar and hydroxide ion; similar results were obtained for the oxidation of D-glucose with cupric ion complexed as the picolinate. The oxidation seems to proceed via a chelated cuprous complex of the enediol.[1] Methods for the quantitative determination of reducing sugars are based on oxidation with hot, alkaline solutions of copper salts (for example, the Soldaini and Fehling reagents). The oxidation products are, in general, monobasic acids having one to six carbon atoms, accompanied by oxalic acid, carbon dioxide, and lactic acid.

The kinetics of the Cu(II) oxidation of D-glucose[187] and D-galactose[188] under acidic conditions (pH 4–5 and 110 °C), and the kinetics of oxidation of L-ascorbic acid by Cu(II) at different pH values have been reported.[189]

In ammoniacal solutions of copper salts, the oxidation products are likely to contain nitrogen; thus, hexoses give oxalic acid, imidazoles, hydrogen cyanide, and urea. Kinetic studies have been reported for the reaction of Cu(II) in the presence of ammonia with maltose, lactose, melibiose, and cellobiose.[190] For the oxidation by tetraamminecopper(II) in ammoniacal and buffered media the rate of reaction is first order in disaccharide concentration, order one-half in ammonia concentration, but it is independent of Cu(II) concentration. The reaction rate is decreased by the addition of ammonium chloride, because of the common ion effect. These kinetics suggested mechanisms involving an intermediate enediolate ion, with the rate of reaction being equal to the rate of enolization.[191] A similar mechanism has been proposed for the oxidation of D-fructose by a copper–pyridine complex in an excess of pyridine.[192]

3. Silver Oxide

The oxidation of carbohydrates by silver oxide at 50 °C (in water or potassium hydroxide) and the use of alkaline silver solutions for the detection of spots on paper chromatograms have been summarized in Ref. 1 (p. 1149). That review also describes common uses of the Fétizon reagent (silver carbonate suspended on Celite)[193] for oxidizing different types of sugar derivatives. Silver(II) picolinate has been employed as an oxidant for isolated hydroxyl groups;[194] with this reagent, 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose was converted into the corresponding 1,4-lactone, and methyl 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranoside into the L-*lyxo*-hexofuransid-5-ulose derivative.

4. Sulfite Pulping

The sulfite process for delignification of wood in the paper industry involves heating with acidic sulfite solutions at elevated temperatures under pressure. Under such conditions, oxidation occurs to a certain extent, and presumably, the sulfite is partly reduced to sulfide. The composition of the liquors resulting from the treatment of cellulose and hemicelluloses, and alditols with sulfite in acid medium has been described (Ref. 1, p. 1150).

5. Wet Combustions

Oxidations of carbohydrates conducted under strongly acidic or strongly alkaline conditions are quite drastic, often completely degrading the substrate to carbon dioxide and water. Extremes of pH enhance either (a) the effectiveness of the oxidant by converting it into a stronger Lewis acid (at low pH), or (b) the nucleophilicity of the organic substrate by deprotonating it to an anion (or carbanion) (at high pH). The high electron density of the latter, negatively charged species facilitates the removal of either a hydride ion or a hydrogen atom, and expedites electron transfer to the oxidant.

The effects of such oxidants as a mixture of potassium iodate and dichromate in concentrated sulfuric and phosphoric acids (van Slyke reagent), hot solutions of chromic acid, and acidic solutions of ceric sulfate, permanganate, periodate, and hyperoxidized transition metals on a number of sugar derivatives has been described (Ref. 1, pp. 1151–1153).

XIII. Enzymatic and Microbial Oxidations

Fermentative processes are of considerable value for the production of useful organic chemicals from carbohydrate precursors. Large amounts of acetic acid, acetone, butanol, citric acid, ethanol, D-gluconic acid, lactic acid, and L-sorbose are made industrially by fermentation. In fermentative processes, oxidizing as well as reducing conditions may be employed, depending on the product desired. Laboratory and industrial preparation of many other substances, such as glycols, have been carried out by using enzymes.

Microorganisms exhibit a marked specificity in their choice of substrates, and in the reaction products. This property is useful for the qualitative and quantitative determination of sugars, as well as for the identification of microorganisms. The formation of glycuronic, aldonic, and glyculosonic acids, and glycosuloses is considered in the preceding Chapter and the bacterial oxidations of aldoses to 2- or 5-hexulosonic, or 2,5-dihexulosonic acids, as well as the formation of hexulose derivatives, have been described in detail (Ref. 1, pp. 1153–1156). Enzymatic approaches to the synthesis of mono- and oligosaccharides and related structures, including those involved in carbohydrate recognition,[195] as well as the oxidations of polyols to polyhydroxyaldehydes by enzymes, and the useful applications of enzymatic oxido–reductions in organic synthesis[196] have been reviewed.

Alditols are oxidized by certain microorganisms; for example, *Acetobacter suboxydans* converts D-mannitol into D-fructose; the oxidation may occur

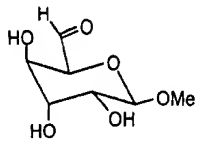
on either C-2 or C-5 because the two atoms are related by symmetry. Isbell *et al.*[197] used isotopically labeled D-mannitol to prove that dissociation of the carbon–hydrogen bond at C-2 (or C-5) is the rate-determining step.

The enzyme glucose oxidase (EC 1.1.3.4), also called *notatin*, catalyzes the oxidation of D-glucose by molecular oxygen to D-gluconic acid. It has been isolated from various molds, especially *Aspergillus niger* and *Penicillium glaucum*. The enzyme is highly specific for β-D-glucopyranose.[198] As the initial reaction product is D-glucono-1,5-lactone, the pyranose ring remains intact, as with bromine oxidation; hydrogen peroxide is also formed.

Glucose oxidase was initially considered to act as an oxidase, but experiments with ordinary molecular oxygen and water enriched with ^{18}O showed that the action is that of a dehydrogenase, which catalyzes the transfer of two hydrogen atoms from D-glucose to gaseous oxygen.[199] The enzyme is commonly used for determining D-glucose, and it has been used in a method for determining the aeration capacity of fermentation tanks.[200] It has also found use in application as a glucose sensor in diabetes control.[201]

A purified D-glucose dehydrogenase, isolated from animal liver, catalyzes the oxidation of D-glucose to D-gluconic acid.[202] A coenzyme (either nicotinamide adenine dinucleotide or its 2′-phosphate) is necessary for the oxidation. The reaction is reversible, and is specific for β-D-glucopyranose; it does not proceed with the α-D anomer, and it occurs only slowly with D-xylose.

D-Galactose oxidase (EC 1.1.3.9) removes the *pro-S* hydrogen atom[203] from C-6 of D-galactopyranose derivatives to produce initially the D-*galacto*-hexodialdo-1,5-pyranose analogues.[204] Thus, in the case of methyl β-D-galactopyranoside, the hexodialdo-1,5-pyranose (**63**) has been characterized, after acetylation, in a dimeric form (**64**). Simultaneously, O_2 is reduced to H_2O_2, which in the presence of the enzyme catalase is decomposed to H_2O and O_2. D-Galactose oxidase is produced by numerous species of fungi, but it is commonly obtained from *Dactylium dendroides*. The kinetic solvent isotope effect of the enzyme isolated from this microorganism suggests that one electron of O_2 is transferred to a transition state that is stabilized by a hydrogen bond from water bound to Cu(II) in the active site[205] (Scheme 29).



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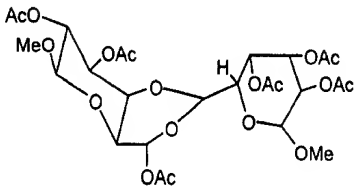


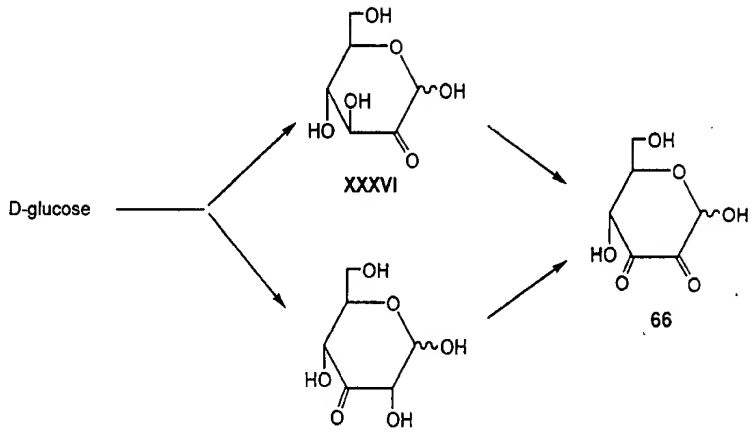
64

SCHEME 29

Galactose oxidase is specific for D-galactose, but it also oxidizes some simple derivatives and various oligosaccharides containing galactose at the nonreducing end. Alditols have been successfully oxidized to the corresponding sugar by galactose oxidase.[206] The oxidation of D-[6-^{3}H]galactose by this enzyme showed a large kinetic isotope effect. As the unlabeled substrate is oxidized faster, material enriched in the labeled component was obtained upon incomplete oxidation of partially labeled starting galactose.[207]

Rogers and Thompson[208] used the action of this enzyme, and subsequent oxidation by bromine, to effect the conversion of a galactomannan into a galacturonomannan; a similar sequence has been used with glycoproteins as a method for linkage analysis.[209]

Characteristic for wood-degrading fungi seems to be the growing family of pyranose 2-oxidases (glucose-2-oxidases, EC 1.1.3.10), enzymes that act as a C-2 specific oxidase of several aldopyranoses,[210] with D-glucose being the favored substrate. The product of oxidation is the dicarbonyl monosaccharide D-*arabino*-hexos-2-ulose, which plays an important role in sugar metabolism of numerous wood-degrading basidiomycetes, such as *Oudemansiella mucida*.[211] Also, the quinone-dependent sugar oxidoreductase, pyranose dehydrogenase purified from *Agaricus bisporus* catalyzed the C-2 or C-3 oxidation of D-glucose to D-*arabino*-hexos-2-ulose (**36**) and, preferentially, D-*ribo*-hexos-3-ulose (**65**). The two aldoketoses accumulate transiently and are finally converted into the same end-product, D-*erythro*-hexose-2,3-diulose (**66**).[212] D-Galactose is exclusively oxidized at C-2 to produce D-*lyxo*-hexos-2-ulose (Scheme 30).



65

SCHEME 30

Incubation of D-xylose with an aqueous solution of bovine lens protein gave both xylitol and xylonic acid. Studies of the reaction under a variety of conditions suggest that both the reduction and oxidation reactions are protein (possibly enzyme) catalyzed and appear to be unique to lens protein.[213]

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